Kiedy napromieniać węzły chłonne w raku stercza ?

Piotr Milecki

Oddział Radioterapii Onkologicznej I i Zakład Radioterapii I
Wielkopolskie Centrum Onkologii
Poznań
Katedra Elektroradiologii, Uniwersytet Medyczny
Poznań

Wprowadzenie

RT układu chłonnego ?

cN0 Choroba mikroskopowa ???

- Bardzo małe i małe ryzyko progresji biochemicznej
- **Pośrednie ryzyko progresji biochemicznej**
- **Wysokie i bardzo wysokie ryzyko progresji biochemicznej**

N+ Choroba mikroskopowa/ makroskopowa ???

- **nie leczony - przerzut (obrazowanie): cN+**
- **po RP - przerzut (raport patologiczny): pN+**
- **po RT lub RP - przerzut (obrazowanie): cN+**

LN

- **cN1** – przerzut zdefiniowany na podstawie obrazowania przed RP lub RT;

implikacje kliniczne – zwykle duży guz – większe ryzyko niepowodzenia, większa liczba N+

„unfavorable category“

- **cN0** - przed elektywną RT w grupie wysokiego ryzyka
- **pN1** – przerzut zdefionawny w ocenie histopatologicznej materiału pooperacyjnego (**cN0**) – przerzut nie widoczny w badaniu obrazowym przed RP.

Implikacje kliniczne - mniejsze zaawansowanie nowotworu = mniej komórek nowotworowych

„favorable category”

Implikacje dla RT

W przypadku cN0/pN1 prawdopodobieństwo wyjałowienia nowotworu RT może być znacząco większe.

Liczba przerzutowych węzłów

- 1 węzeł chłonny vs 2 węzły chłonne i > vs 3 i > węzły chłonne
- Czy potrzeba jest zmiana klasyfikacji TNM ?

RP + PLND jeżeli > 2 %

PLOS ONE

RESEARCH ARTICLE

Single Positive Lymph Node Prostate Cancer Can Be Treated Surgically without Recurrence

Dae Keun Kim[1,2], Kyo Chul Koo[3], Ali Abdel Raheem[3,4], Ki Hong Kim[5], Byung Ha Chung[3], Young Deuk Choi[3], Koon Ho Rha[3]*

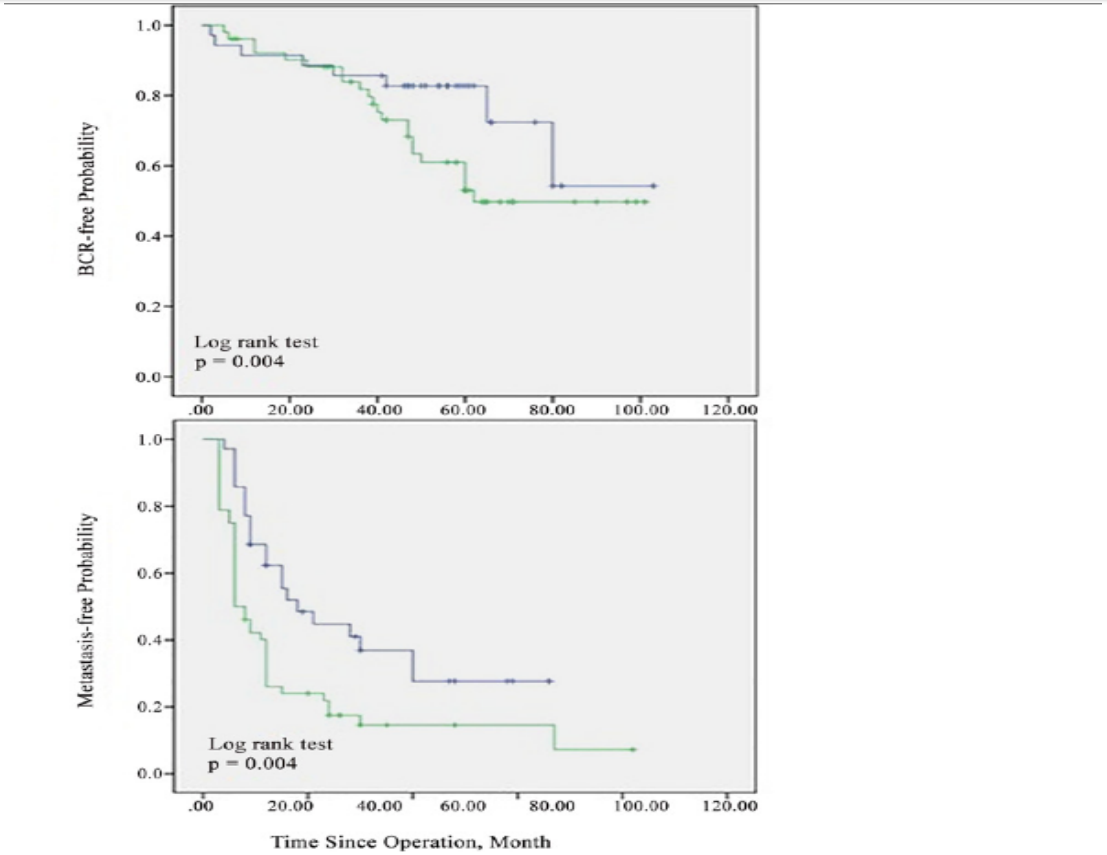


Fig 1. Kaplan-Meier curve for biochemical recurrence-free survival and metastasis-free survival by the number of positive lymph nodes. Blue line = one positive lymph node; green line = two or more positive lymph nodes.

- **Historycznie stwierdzano przerzuty u 20-40% operowanych chorych;**

(Fowler JE, Jr, Whitmore WF, Jr. The incidence and extent of pelvic lymph node metastases in apparently localized prostatic cancer. Cancer. 1981;47:2941-5.).

Zincke H. Extended experience with surgical treatment of stage D1 adenocarcinoma of prostate. Significant influences of immediate adjuvant hormonal treatment (orchiectomy) on outcome. Urology. 1989;33(5 Suppl):27-36.

- **Obecnie stwierdza się < 10% wszystkich operowanych chorych.**

Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am. 2001;28:555-65.

Palapattu GS, Allaf ME, Trock BJ, et al. Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term followup. J Urol. 2004;172(5 Pt 1):1860-4.

Petros JA, Catalona WJ. Lower incidence of unsuspected lymph node metastases in 521 consecutive patients with clinically localized prostate cancer. J Urol. 1992;147:1574-5.

- Niemniej taki spadek jest wynikiem migracji stopnia zaawansowania i kwalifikowania do operacji chorych z niskim i pośrednim ryzykiem progresji. W tych grupach chorych ryzyko przerzutów do układu chłonnego jest niskie.

- Natomiast w grupie wysokiego i bardzo wysokiego ryzyka występownie przerzutów patologicznych (pN1 a cN0), czyli tych które byłyby przedmiotem napromieniania jest już duże; > 15% - 50%.

Przerzut w układzie chłonnym z perspektywy chirurga

- eLND should be performed in all high-risk cases, because the estimated risk for positive lymph nodes is 15-40%.
- Besides being a staging procedure, pelvic LND/eLND can be curative, or at least beneficial, in a subset of patients with limited lymph node metastases
- Obecnie standardem jest extended Lymphadenectomy, a nawet supra-extended LN ?
- ewolucja poglądów – wiedzy na temat znaczenia leczenia przerzutów w układzie chłonnym.

Table Outcomes for Patients Treated With Various Combinations of Androgen Deprivation Therapy and Local Therapies for Lymph Node–Positive Prostate Cancer

Author	N	Follow-up (yr)	OS at 5 yr	OS at 10 yr	PCCS at 5 yr	PCCS at 10 yr	PFS at 5 yr	PFS at 10 yr	bFS at 5 yr	bFS at 10 yr
No Treatment (delayed ADT)										
Schroder et al (EORTC 30846)	115	13	64%	25%	72%	44%				
Systemic Treatment Alone (immediate ADT)										
Schroder et al (EORTC 30846)	119	13	68%	30%	77%	48%				
Frohmuller et al (Univ of Würzburg)	87	4.7	60%	30%			35%	15%		
Engel et al[a] (Munich Cancer Registry)	250	5.3	60%	28%						
Zagars et al (MDACC)	183	9.4	83%	46%					41%	25%
Radical Prostatectomy Alone										
Messing et al (ECOG 3886)	51	11.9	75%	55%	75%	55%	28%	15%		
Bader et al (Univ of Bern)	87	3.7	74%		74%					
Radical Prostatectomy With Immediate ADT										
Messing et al (ECOG 3886)	47	11.9	90%	80%	95%	90%	82%	70%		
Frohmuller et al (Univ of Würzburg)	52	4.3	74%	51%			62%	36%		
Engel et al[a] (Munich Cancer Registry)	688	6.7	84%	64%						
Boorjian et al[b] (Mayo Clinic)	507	10.3			94%	86%			69%	56%
Schiavina et al[c] (Univ of Bologna)	98	5.7	84%	64%	86%	72%				
Briganti et al (Vita-Salute and Mayo)	247	8.6	82%	55%	88%	70%				
Radiation Therapy Alone										
Hanks et al (RTOG 7506)	90	10	63%	29%					31%	7%
Lee et al (LDS Hospital, Utah)	36	15	50%	20%	51%	25%	32%	10%		
Lawton et al (RTOG 8531)	54	6.5	60%	31%						
Radiation Therapy With Immediate ADT										
Lawton et al (RTOG 8531)	77	6.5	70%	47%						
Zagars et al (MDACC)	72	6.2	92%	67%					91%	80%
Whittington et al (UPenn)	45	3.5	92%						73%	
Radical Prostatectomy Followed by Adjuvant RT and ADT										
Briganti et al (Vita-Salute and Mayo)	117	8	90%	74%	95%	86%				

Profilaktyczna
RT układu chłonnego ?

cN0

Dlaczego nie ma zysku z WPRT ?

Dlaczego nie wykazano zysku z WPRT ?

- Dobór chorych – kwalifikacja do leczenia
- Dawka (Tu, LN)
- Objętość Napromieniana
- HT

RCT oceniające WPRT

[1] Lawton CA, DeSilvio M, Roach M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of **RTOG 94-13**, with emphasis on unexpected hormone/ radiation interactions. Int J Radiat Oncol Biol Phys 2007;69:646–55.

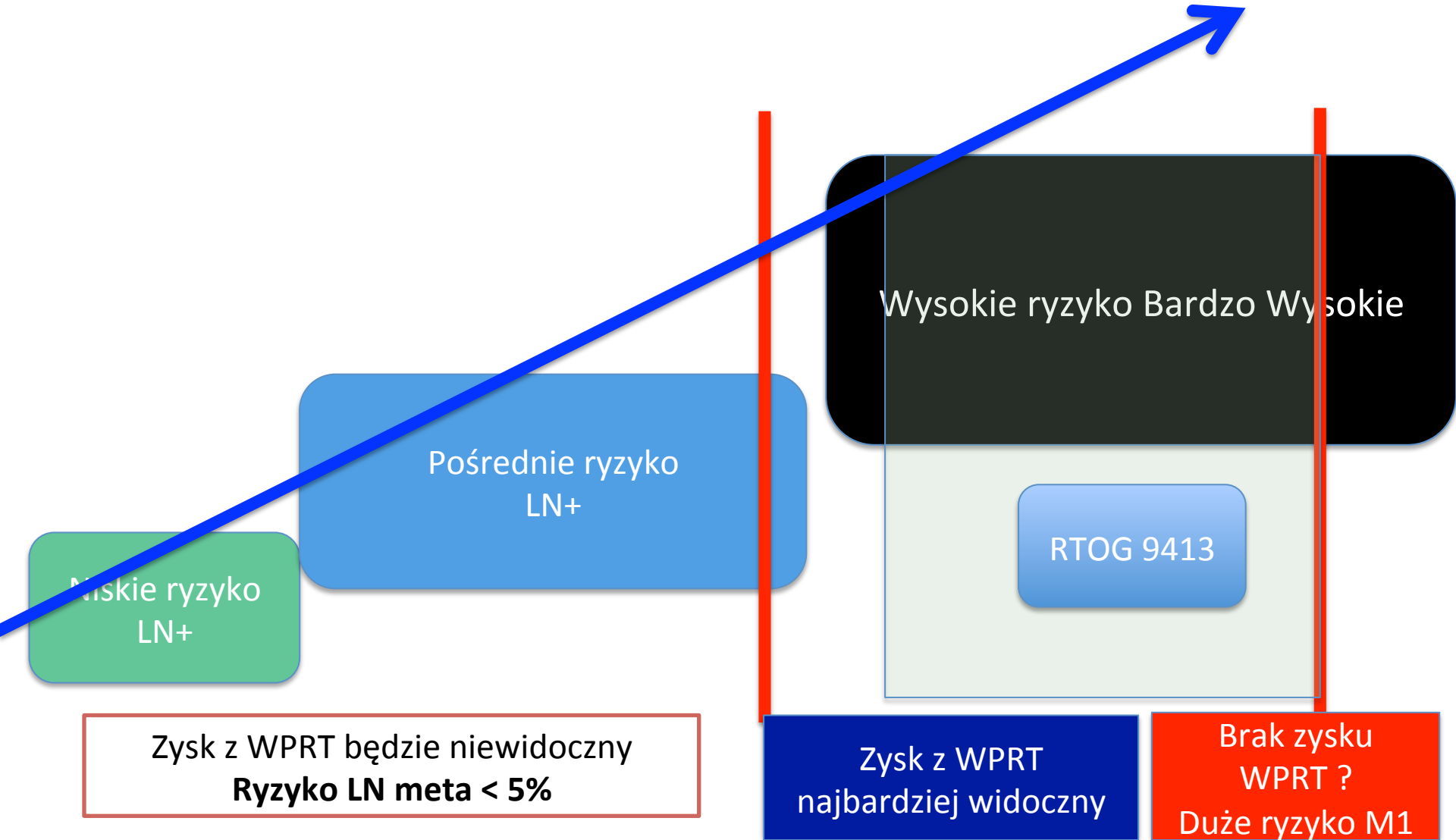
[2] Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of **GETUG-01**. J Clin Oncol 2007;25:5366–73.

[3] Asbell S, Krall J, Pilepich M, et al. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of **RTOG 77-06**. Int J Radiat Oncol Biol Phys 1988;15:1307–16.

Przyczyny braku zysku z WPRT ?

Dobór chorych do WPRT

heterogenna grupa



Mało efektywna RT w ognisku pierwotnym

Dawka RT w RCTs: 66 Gy – 70 Gy

Poprawa efektywności RT w ognisku pierwotnym jest warunkiem niezbędnym aby wykazać zysk z WPRT.

W sytuacji kiedy efektywność RT jest niska w ognisku pierwotnym wówczas to niepowodzenie determinuje postrzeganie niepowodzenia w leczeniu.

Mało efektywna diagnostyka układu chłonnego

Diagnostyka Przed leczeniem:

- **cN0 w rzeczywistości cN1**
- **cN0 w rzeczywistości cN0**

Dawka Elektywna RT

- 45 Gy – 50 Gy; dobra elektywna Dawka w H&N
- 45 Gy – 50 Gy; w raku stercza?

ADT + RT > RT

ADT jako dodatkowa dawka do RT ?

- Czy ADT + RT również działa w układzie chłonnym ?
- Jeżeli tak, to: 45 Gy – 50 Gy + **X Gy (ADT) ?**

Napromieniana Objętość !!!

- Zasłonowe
- Przedkrzyżowe
- Okołoodbytnicze
- Biodrowe zew/wew
- **Biodrowe wspólne**
- **Dolne około-aortalne !!**

- **CTV; naczynia/węzły z +/-7 mm marginesem**

- Wyzwanie w przypadku IGRT; RT jest orientowana na Stercz, a istnieje niezależna ruchomość Stercza względem Węzłów.
- **Przygotowanie chorego do RT** – im mniejsza ruchomość stercza tym dokładniejsza RT układu chłonnego

RTOG GU Radiation Oncology Specialists Reach Consensus on Pelvic Lymph Node Volumes for High-Risk Prostate Cancer

Colleen A.F. Lawton, M.D., Jeff Michalski, M.D., Issam El-Naqa, Ph.D., Mark K. Buyyounouski, M.D., W. Robert Lee, M.D., Cynthia Menard, M.D., Elizabeth O'Meara, M.D., Seth A. Rosenthal, M.D., Mark Ritter, M.D., Michael Seider, M.D.

Górna granica bardzo ważna !!!

Consensus was obtained resulting in computed tomography image-based pelvic lymph node CTVs. Based on this consensus, the pelvic lymph node volumes to be irradiated include: distal common iliac, presacral lymph nodes (S_1-S_3), external iliac lymph nodes, internal iliac lymph nodes, and obturator lymph nodes. Lymph node CTVs include the vessels (artery and vein) and a 7-mm radial margin being careful to "carve out" bowel, bladder, bone, and muscle. Volumes begin at the L5/S1 interspace and end at the superior aspect of the pubic bone. Consensus on dose–volume histogram constraints for OARs was also attained.

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European Association of Urology

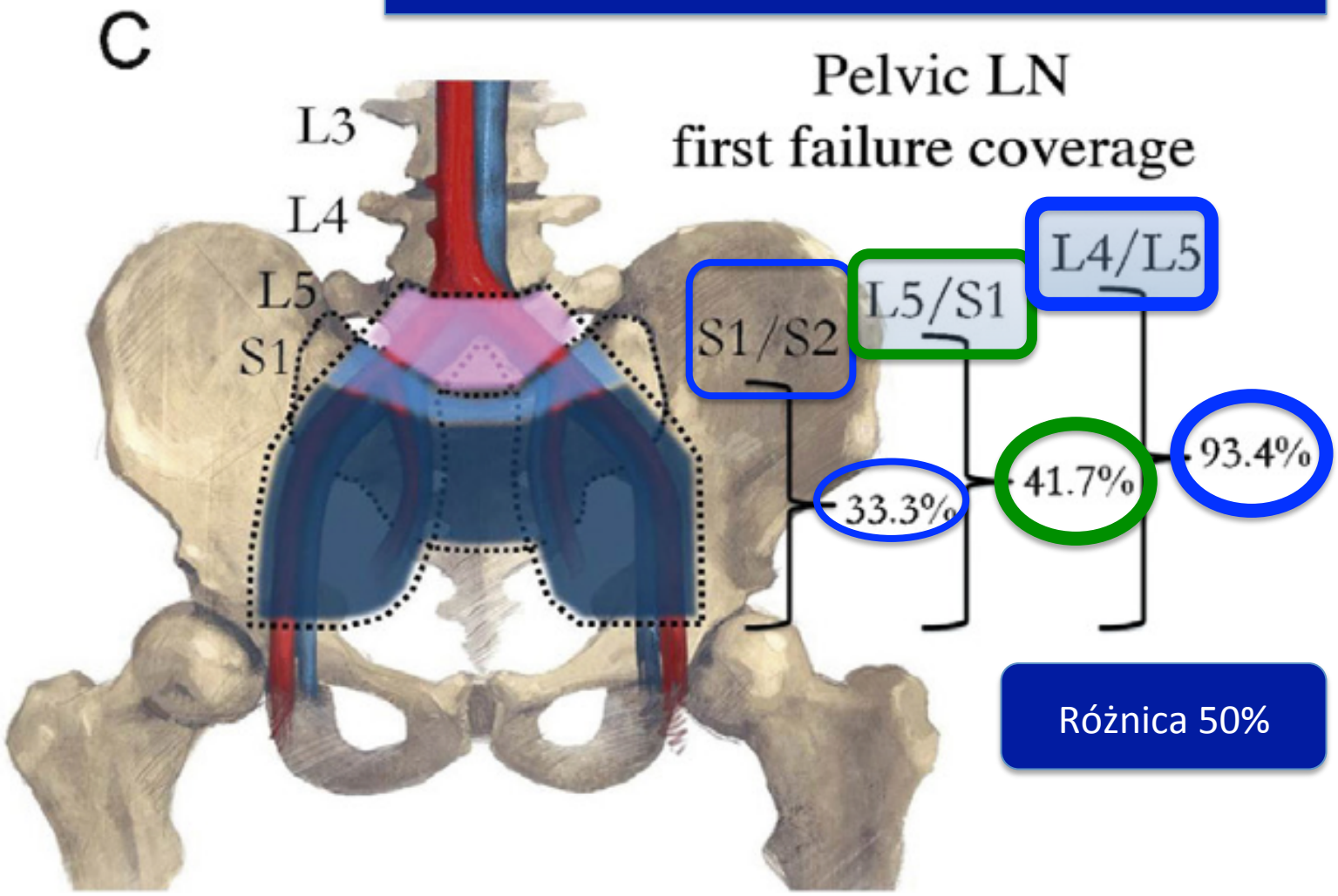
Platinum Priority – Prostate Cancer
Editorial by Cesare Cozzarini on pp. 44–45 of this issue

Patterns of Lymph Node Failure after Dose-escalated Radiotherapy: Implications for Extended Pelvic Lymph Node Coverage

Daniel E. Spratt [a,b,], Hebert A. Va
Joseph R. Osborne [c], Xin Pei [a], Mic

[a] Department of Radiation Oncology, Memorial Sloan Michigan, Ann Arbor 48109, USA; [c] Department of Rad

- 156 chorych (przerzut LN)
- cN0; TK/MRI/PET TK/MRI/PET
- RT bez WPRT
- ADT
- FU- 8.9 lat



Różnica 50%

Distribution of prostate nodes: a PET/CT-derived anatomic atlas of prostate cancer patients before and after surgical treatment

- Nina-Sophie Hegemann[1] Email author,
- Vera Wenter[2],
- Sonja Spath[1],
- Nadia Kusumo[1],
- Minglun Li[1],
- Peter Bartenstein[2],
- Wolfgang P. Fendler[2],
- Christian Stief[3],
- Claus Belka[1] and
- Ute Ganswindt[1]

Radiation Oncology201611:37

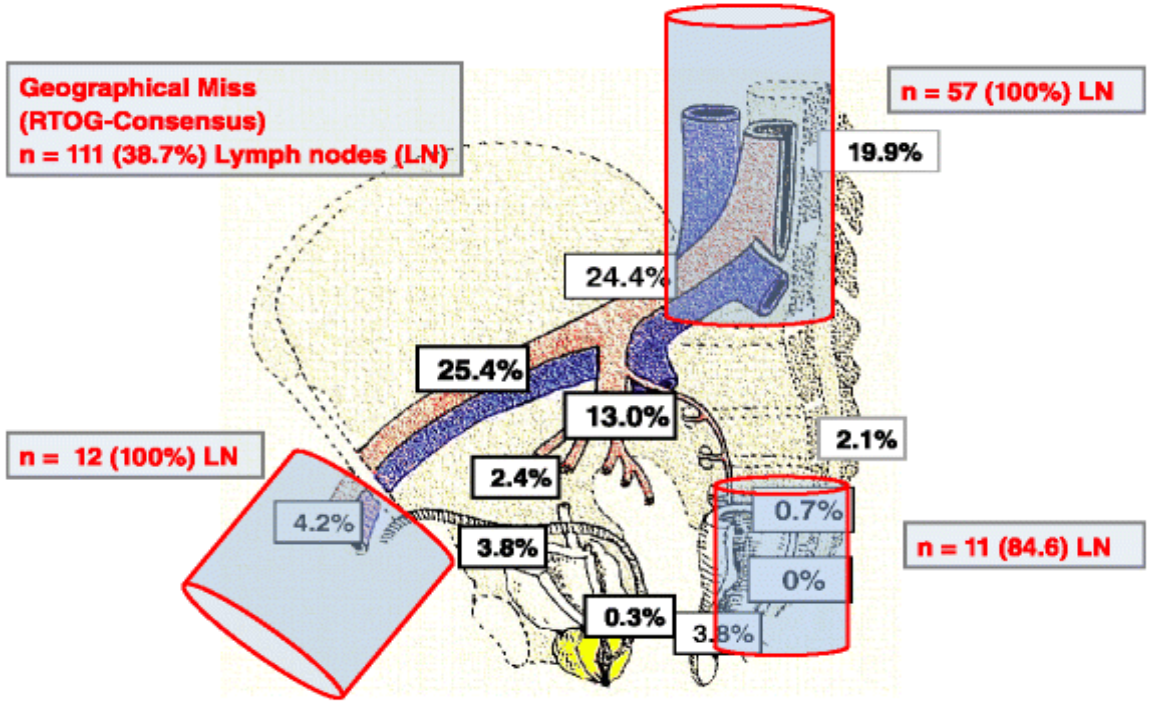


Fig. 2

Schematic distribution of PET positive lymph nodes in all patients (n=119) Anatomical regions and distribution (percentages in *white square frames*) of all detectable PET positive lymph nodes (n=287). Main regions of geographical misses (*red*), when RTOG-Consensus (Lawton et al. [5]) for standard CTV delineation is used

Gdzie powinna być górna granica WPRT ?

L4/L5

Jak efektywna jest WPRT ?

Author	Institution		Key Findings
Seaward[278,279]	UCSF	Retrospective single-institutional analysis of patients undergoing prostate-only or WPRT with and without hormonal therapy	WPRT defined at superior border L5-S1. Noted WPRT associated with improved PSA control rate. Greatest benefit seen for those with risk between 15% and 30%.
Pan[280]	University of Michigan	Compared men treated with definitive 3D-CRT ($N = 1832$) divided into three categories based on the estimated risk (Partin Table) of LN involvement: 0%-5%, >5%-15%, and >15%.	Significant benefit for WPRT in men with risk of LN involvement of 5%-15% with an improved 2-year PSA control rate, 90.1% vs. 80.6% ($P = 0.02$).
Roach[140]	RTOG	Phase randomized trial III (N ~1200) comparing sequence of hormonal therapy and role of WPRT vs. prostate-only radiotherapy. Primary endpoint: PFS (including PSA, clinical failure, death from any cause).	WPRT associated with improvement in PFS when preceded by CAB but not when administered before CAB
Jacob[281]	Fox Chase Cancer Center	Retrospective analysis of patients with risk +LN >15% treated with WPRT vs. partial pelvic radiotherapy, or prostate-only fields ($N = 420$). Concluded radiation dose was the major determinant of PSA control in patients with a LN risk >15%, with no benefit to pelvic radiotherapy or hormonal therapy.	None of the patients received WPRT (defined as superior border L5-S1) as defined by RTOG 9413. All patients' pelvic fields would have been included in prostate-only arm of RTOG 9413.
Spiotto[145]	Stanford	Retrospective analysis of postoperative patients undergoing prostate-only or WPRT with and without hormonal therapy.	Use of WPRT associated with an improvement in PSA control rate in the setting of salvage radiotherapy, with greatest benefit seen in patients with adverse features
Pommier[284]	Multicenter French Trial	444 patients with T_{1b}-$T_3N_0M_0$ randomized to 66-70 Gy to prostate +/– 46 Gy to pelvis with the superior border set to S1/S2. Radiotherapy preceded by 4-8 months of CAB is some "high-risk" patients (>T_3, GS >7, or PSA >3 × normal). Most patients had LN risk <15% (55%) using Roach formula.	*None* of the patients received WPRT (defined as top L5-S1); most were low-risk for LN involvement (median PSA 12, ~25% T_3, and ~10% GS 8-10), and some did not receive CAB.
Da Pozzo[143]	Italy	Retrospective study of 250 consecutive patients with positive lymph nodes. Compared outcomes in 129 men treated with WPRT (51.6%) and ADT and 121 patients (48.4%) received ADT alone.	Multivariable analysis use of WPRT and the number of positive LNs were major predictors of PSA control ($P = 0.002$ and $P = 0.003$) and cause-specific survival ($P = 0.009$ and $P = 0.01$).
Aizer[144]	Yale	Retrospective review of 277 consecutive patients with estimated risk of LN involvement >15%.	After adjusting for other factors, WPRT group had improved 4-year biochemical control rate (69.4% vs. 86.3%).
Milecki[536]	Greater Poland Cancer Center	Retrospective analysis including men with high-risk disease ($N = 162$) with and without WPRT.	The 5-year actuarial CSSs were A = 90% and B = 79% ($P = 0.01$) and PSA control rates 52% versus 40% ($P = 0.07$), respectively.

Whole Pelvis Versus Prostate-Only Radiotherapy With or Without Short-Course Androgen Deprivation Therapy and Mortality Risk

Lior Z. Braunstein, Ming-Hui Chen, Daniel E. Dosoretz, Sharon A. Salenius, Michael J. Katin, Akash Nanda, Anthony V. D'Amico

Background

The purpose of the study was to determine whether the extent of prostate radiotherapy (ie, whole-pelvic radiotherapy [WPRT] vs. prostate and seminal vesicle radiotherapy [PSVRT]) is associated with all-cause mortality (ACM) in men treated with or without androgen deprivation therapy (ADT).

Patients and Methods

A multiple-institution cohort of 3709 prostate cancer patients was prospectively assembled from 1991 to 2006. The median age was 72 years and all patients had T1c-T3N0M0 adenocarcinoma of the prostate. Patients were treated with WPRT or PSVRT followed by a brachytherapy boost, with or without neoadjuvant ADT (median duration, 4.2 months). Seventy percent of patients had unfavorable-risk disease (Gleason score ≥ 7; prostate-specific antigen ≥ 10 ng/mL; or stage ≥ T2b). Cox regression was applied to determine whether the radiation treatment volume affected the risk of ACM. The interaction between radiation volume and ADT use was assessed.

Results

After a median follow-up of 3.3 years, 561 deaths were observed. A decreased risk of ACM was noted with the use of WPRT versus PSVRT (adjusted hazard ratio [AHR], 0.58; 95% confidence interval [CI], 0.38-0.89; $P = .01$), or with ADT use (AHR, 0.71; 95% CI, 0.58-0.90; $P = .004$). However, a combination of WPRT and ADT did not further improve ACM compared with either WPRT alone or PSVRT with ADT. Moreover, there was a significant interaction between the radiotherapeutic treatment volume and ADT (AHR, 1.61; 95% CI, 1.004-2.58; $P = .048$).

Conclusion

Treatment with WPRT or short-course ADT is associated with a decreased risk of ACM, although a combination of the two does not yield greater benefit. This observation suggests a shared mechanism for this risk reduction, which we hypothesize to be via the treatment of micrometastatic disease within the pelvic lymph nodes.

Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):e721-6. doi: 10.1016/j.ijrobp.2010.12.003. Epub 2011 Jan 27.

Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy.

Mantini G[1], Tagliaferri L, Mattiucci GC, Balducci M, Frascino V, Dinapoli N, Di Gesù C, Ippolito E, Morganti AG, Cellini N.

Author information

Abstract

PURPOSE: To evaluate the effect of whole pelvic radiotherapy (WPRT) in prostate cancer patients treated with RT and long-term (>1 year) androgen deprivation therapy (ADT).

METHODS AND MATERIALS: Prostate cancer patients with high-risk features (Stage T3-T4 and/or Gleason score≥7 and/or prostate-specific antigen level≥20 ng/mL) who had undergone RT and long-term ADT were included in the present analysis. Patients with bowel inflammatory disease, colon diverticula, and colon diverticulitis were excluded from WPRT and treated with prostate-only radiotherapy (PORT). Patients were grouped according to nodal risk involvement as assessed by the Roach formula using different cutoff levels (15%, 20%, 25%, and 30%). Biochemical disease-free survival (bDFS) was analyzed in each group according to the RT type (WPRT or PORT).

RESULTS: A total of 358 patients treated between 1994 and 2007 were included in the analysis (46.9% with WPRT and 53.1% with PORT). The median duration of ADT was 24 months (range, 12-38). With a median follow-up of 52 months (range, 20-150), the overall 4-year bDFS rate was 90.5%. The 4-year bDFS rate was similar between the patients who had undergone WPRT or PORT (90.4% vs. 90.5%; p=NS). However, in the group of patients with the greatest nodal risk (>30%), a significant bDFS improvement was recorded for the patients who had undergone WPRT (p=.03). No differences were seen in acute toxicity among the patients treated with WPRT or PORT. The late gastrointestinal toxicity was similar in patients treated with PORT or WPRT (p=NS).

CONCLUSIONS: Our analysis has supported the use of WPRT in association with long-term ADT for patients with high-risk nodal involvement (>30%), although a definitive recommendation should be confirmed by a randomized trial.

Int J Radiat Oncol Biol Phys. 2015 Dec 1;93(5):1052-63. doi: 10.1016/j.ijrobp.2015.09.006. Epub 2015 Sep 18.

Survival Outcomes of Whole-Pelvic Versus Prostate-Only Radiation Therapy for High-Risk Prostate Cancer Patients With Use of the National Cancer Data Base.

Amini A[1], Jones BL[1], Yeh N[1], Rusthoven CG[1], Armstrong H[1], Kavanagh BD[2].

Author information

Abstract

PURPOSE/OBJECTIVES: The addition of whole pelvic (WP) compared with prostate-only (PO) radiation therapy (RT) for clinically node-negative prostate cancer remains controversial. The purpose of our study was to evaluate the survival benefit of adding WPRT versus PO-RT for high-risk, node-negative prostate cancer, using the National Cancer Data Base (NCDB).

METHODS AND MATERIALS: Patients with high-risk prostate cancer treated from 2004 to 2006, with available data for RT volume, coded as prostate and pelvis (WPRT) or prostate alone (PO-RT) were included. Multivariate analysis (MVA) and propensity-score matched analysis (PSM) were performed. Recursive partitioning analysis (RPA) based on overall survival (OS) using Gleason score (GS), T stage, and pretreatment prostate-specific antigen (PSA) was also conducted.

RESULTS: A total of 14,817 patients were included: 7606 (51.3%) received WPRT, and 7211 (48.7%) received PO-RT. The median follow-up time was 81 months (range, 2-122 months). Under MVA, the addition of WPRT for high-risk patients had no OS benefit compared with PO-RT (HR 1.05; P=.100). On subset analysis, patients receiving dose-escalated RT also did not benefit from WPRT (HR 1.01; P=.908). PSM confirmed no survival benefit with the addition of WPRT for high-risk patients (HR 1.05; P=.141). In addition, RPA was unable to demonstrate a survival benefit of WPRT for any subset. Other prognostic factors for inferior OS under MVA included older age (HR 1.25; P<.001), increasing comorbidity scores (HR 1.46; P<.001), higher T stage (HR 1.17; P<.001), PSA (HR 1.81; P<.001), and GS (HR 1.29; P<.001), and decreasing median county household income (HR 1.15; P=.011). Factors improving OS included the addition of androgen deprivation therapy (HR 0.92; P=.033), combination external beam RT plus brachytherapy boost (HR 0.71; P<.001), and treatment at an academic/research institution (HR 0.84; P=.002).

CONCLUSION: In the largest reported analysis of WPRT for patients with high-risk prostate cancer treated in the dose-escalated era, the addition of WPRT demonstrated no survival advantage compared with PO-RT.

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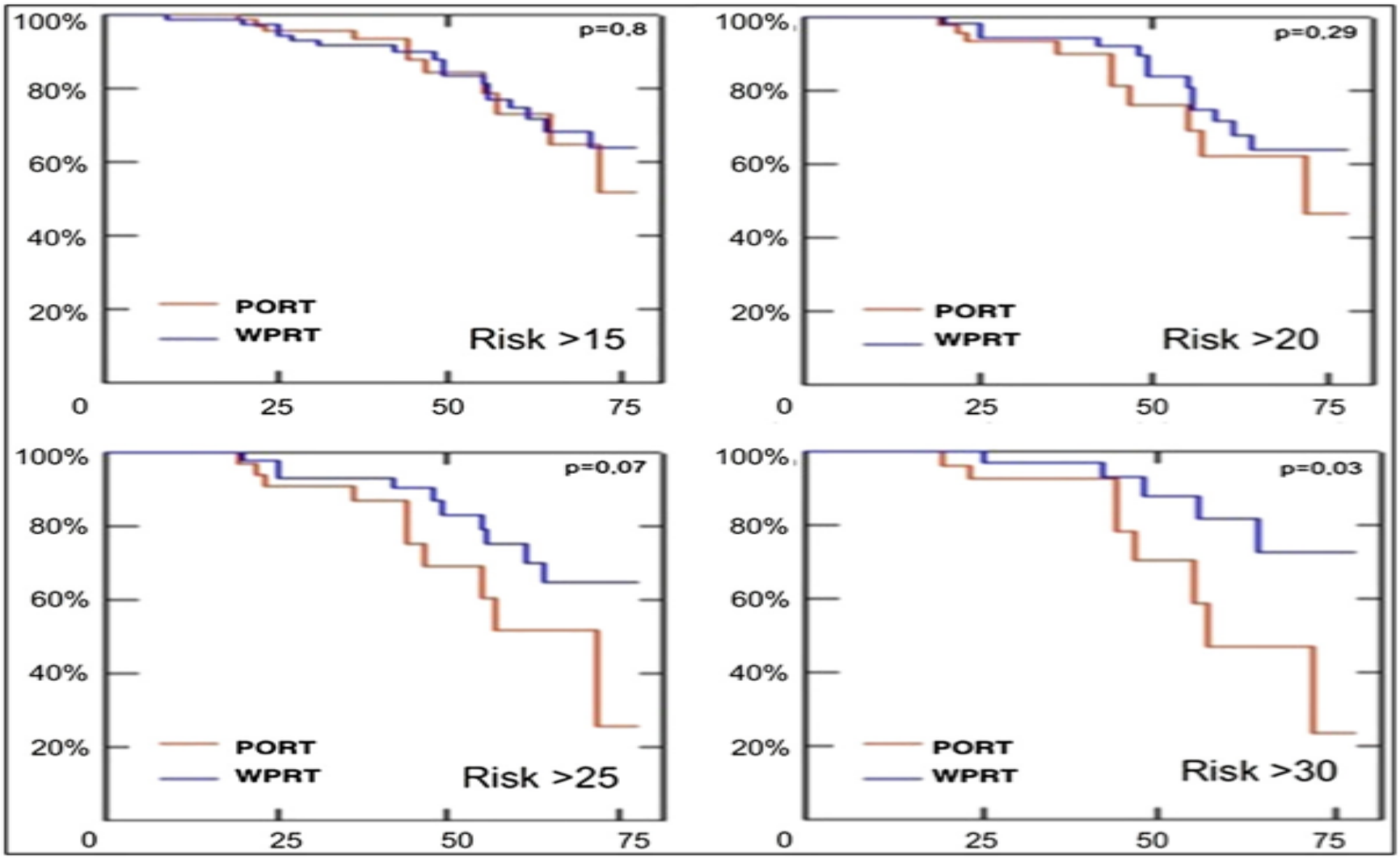
doi:10.1016/j.ijrobp.2010.12.003

CLINICAL INVESTIGATION **Prostate**

EFFECT OF WHOLE PELVIC RADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER TREATED WITH RADIOTHERAPY AND LONG-TERM ANDROGEN DEPRIVATION THERAPY

Giovanna Mantini, M.D.,* Luca Tagliaferri, M.D.,* Gian Carlo Mattiucci, M.D.,*
Mario Balducci, M.D.,* Vincenzo Frascino, M.D.,* Nicola Dinapoli, M.D.,*
Cinzia Di Gesù, M.D.,† Edy Ippolito, M.D.,† Alessio G. Morganti, M.D.,† and Numa Cellini, M.D.*



RTOG 94-13

- 1323 chorych, LN+> 15%, TD= 70 Gy
- Pośrednie & Wysokie ryzyko
- 4 ramiona; PORT v. WPRT, NHT (4 mce) v. AHT (4 mce)

- Whole Pelvis (L5/S1)
- Mini Pelvis (10 cmx 11 cm)
- PO

- **Wykazano wpływ napromienianej objętości:**
  7-year DFS: 40% vs 35% vs 27 % (p= 0.02)
- Brak różnic: OS
- **PFS & BF; NHT + WPRT > NHT + PORT**
- Brak różnic: secondary ca; WPRT v. PORT

RTOG 94-13

- 70% chorych; cT2c lub cT3;
- Dawka całkowita P; 70,2 Gy/ 1,8 Gy < 70 Gy/ 2 Gy
  Słaba efektywność miejscowa RT (dawka), RT bez IGRT

- ADT; tylko 4 mce

- Duża grupa chorych GS (8-10) i cT3 i PSA>20
  Wysokie ryzyko LN+ i również M1 !!!!

- Granica WPRT L5/S4 – błąd geograficzny?

GETUG-01

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Final results of the GETUG-01 randomized study

Pascal POMMIER, Sylvie CHABAUD, Jean Leon LAGRANGE, Pierre RICHAUD, Elisabeth LE PRISE, Jean Philippe WAGNER, Meng Huor HAY, Veronique BECKENDORF, Jean Philippe SUCHAUD, Valerie BERNIER, David PEROL, and Christian CARRIE

Final results: updated in 2015

Tylko 45% chorych ryzyko LN+ > 15%

- Randomized, multicenter phase III study
- Prostate adenocarcinoma – definitive radiotherapy
- T1c-T3 pNx all Gleason Score; all PSA value
- Stratification criteria
  - Investigational site
  - High risk vs. low risk for lymph node involvement

Low Risk	High Risk
T1-T2 and Gleason score = 6 and PSA ≤ 3x the upper normal of the laboratory	T3 and/or Gleason score > 6 and/or PSA > 3x the upper normal of the laboratory

* Study designed in 1997

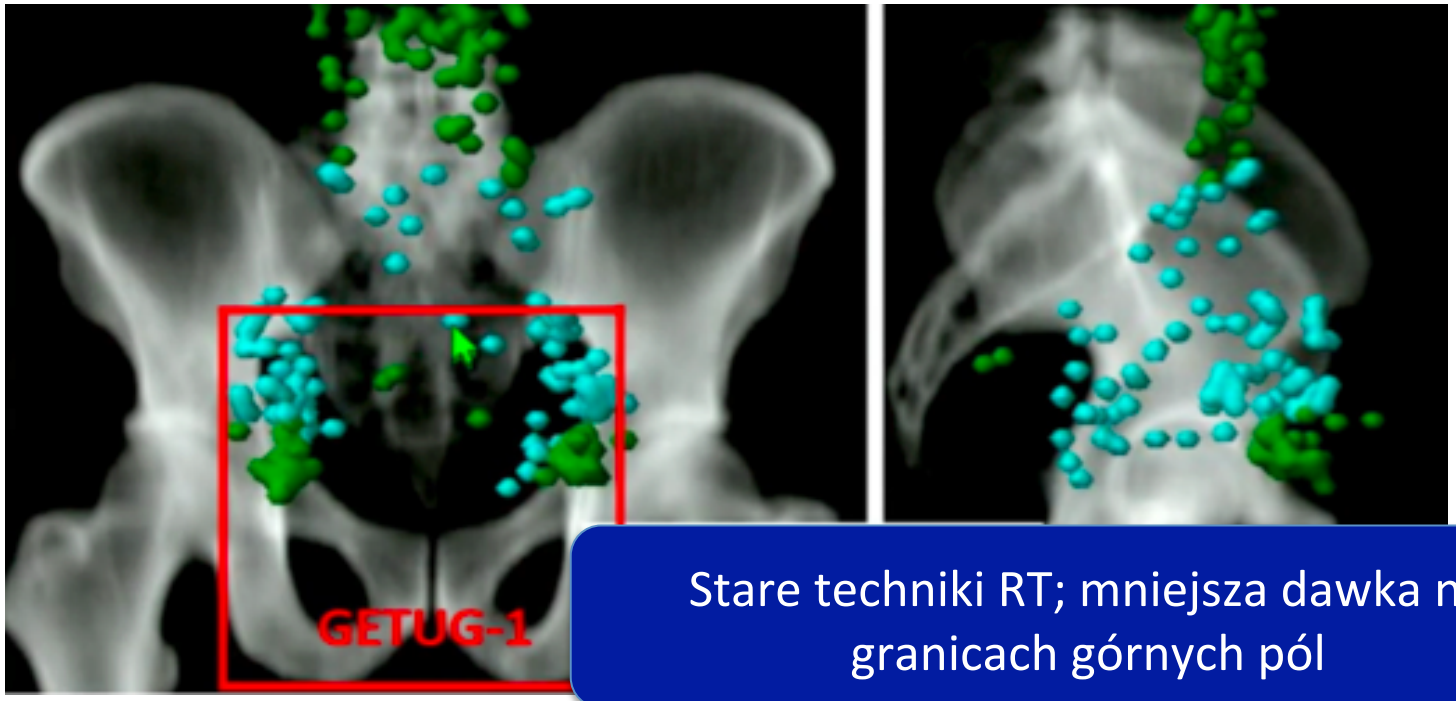
Górna granica WPRT; S1/S2

- Radiotherapy (RT)
  - Pelvic nodes: **46 Gy** ; SV: 46 Gy (up to 60 Gy in case of SV involvement)

Dawka na Stercz; 66 Gy/ 2Gy, 70 Gy od 2000 r.

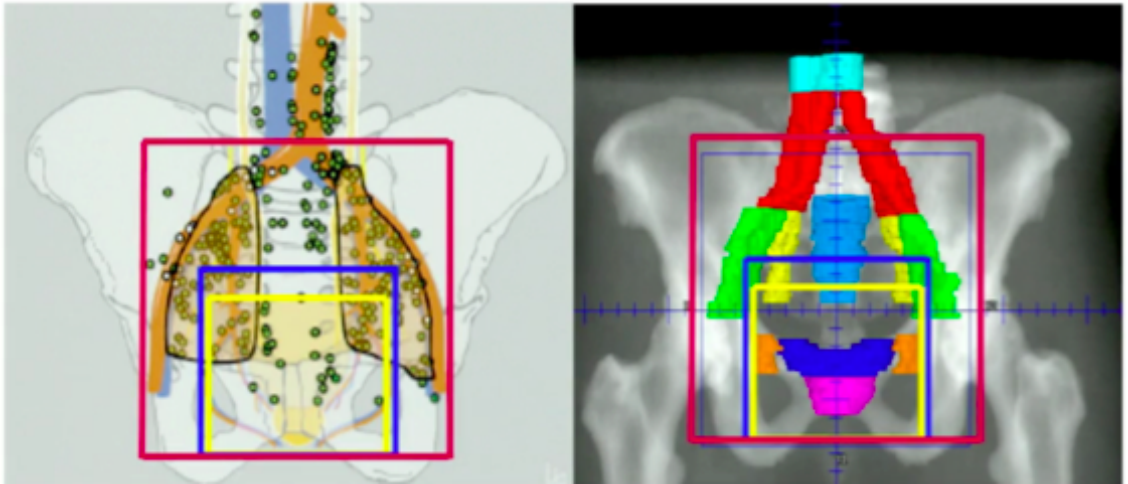
- Hormonal therapy
  - Authorized (not mandatory) **in the high- risk group only**
  - 4-to-8 months neoadjuvant and concomitant HT (LHRH agonist + initial short term anti-androgen administration)

* Study designed in 1997



Stare techniki RT; mniejsza dawka na granicach górnych pól

The Template of the Primary Lymphatic Landing Sites of the Prostate Should be Revisited: Results of a Multimodality Mapping Study. Mattei ... Studer. EAU 53:118-125, 2008

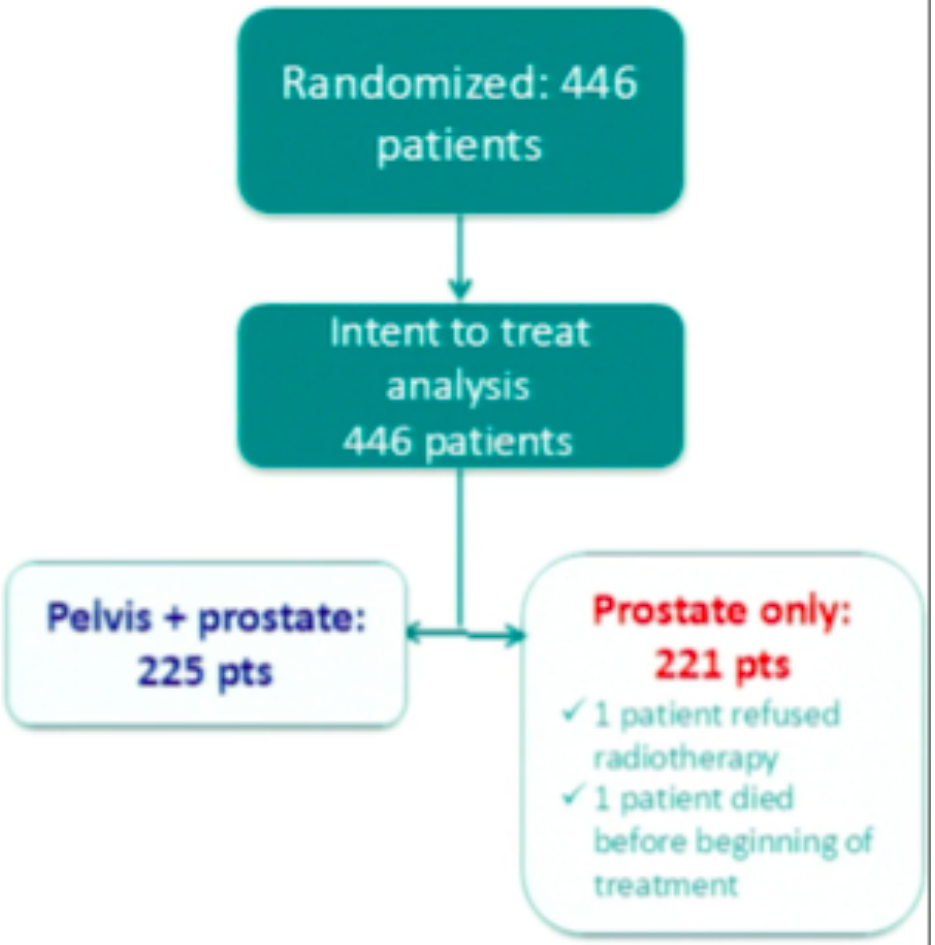


Recruitment and follow-up

- **446 patients** randomized between 12/1998 and 06/2004 within 21 French centers

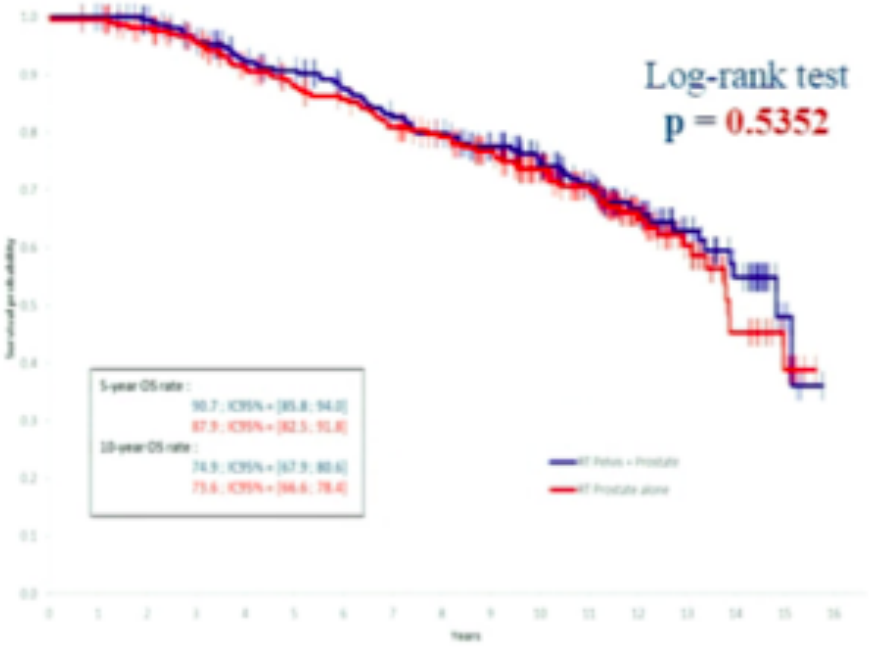
- Median follow-up

  ⇨ **11.4 years** [0.01 – 15.7]

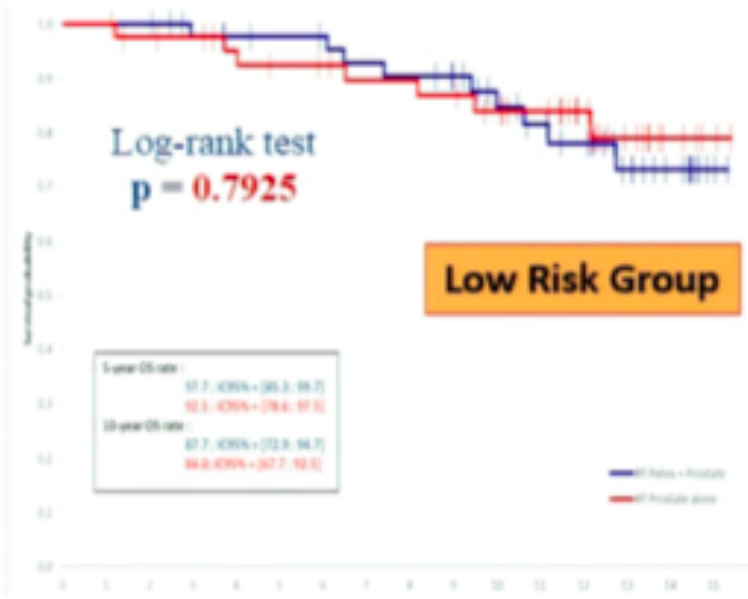


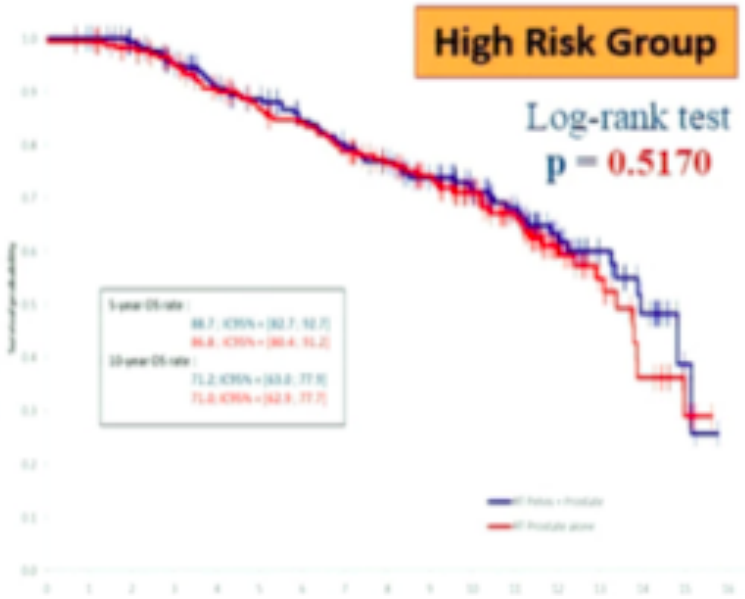
		Pelvis + Prostate (N=225) %	Prostate only (N=225) %	p
Prognostic group *(stratified)*	Low-Risk	21.3	19.9	0.727
	High-Risk	78.7	80.1	
LNI risk *(subgroup analysis)* (Roach Formula*)	< 15%	51.3	56.8	0.364
	15-35%	37.1	34.9	
	> 35%	11.6	8.3	
Hormonal Therapy *(High Risk group only)*		57.5	59.7	0.261

* 2/3 PSA + [(GS-6)*10

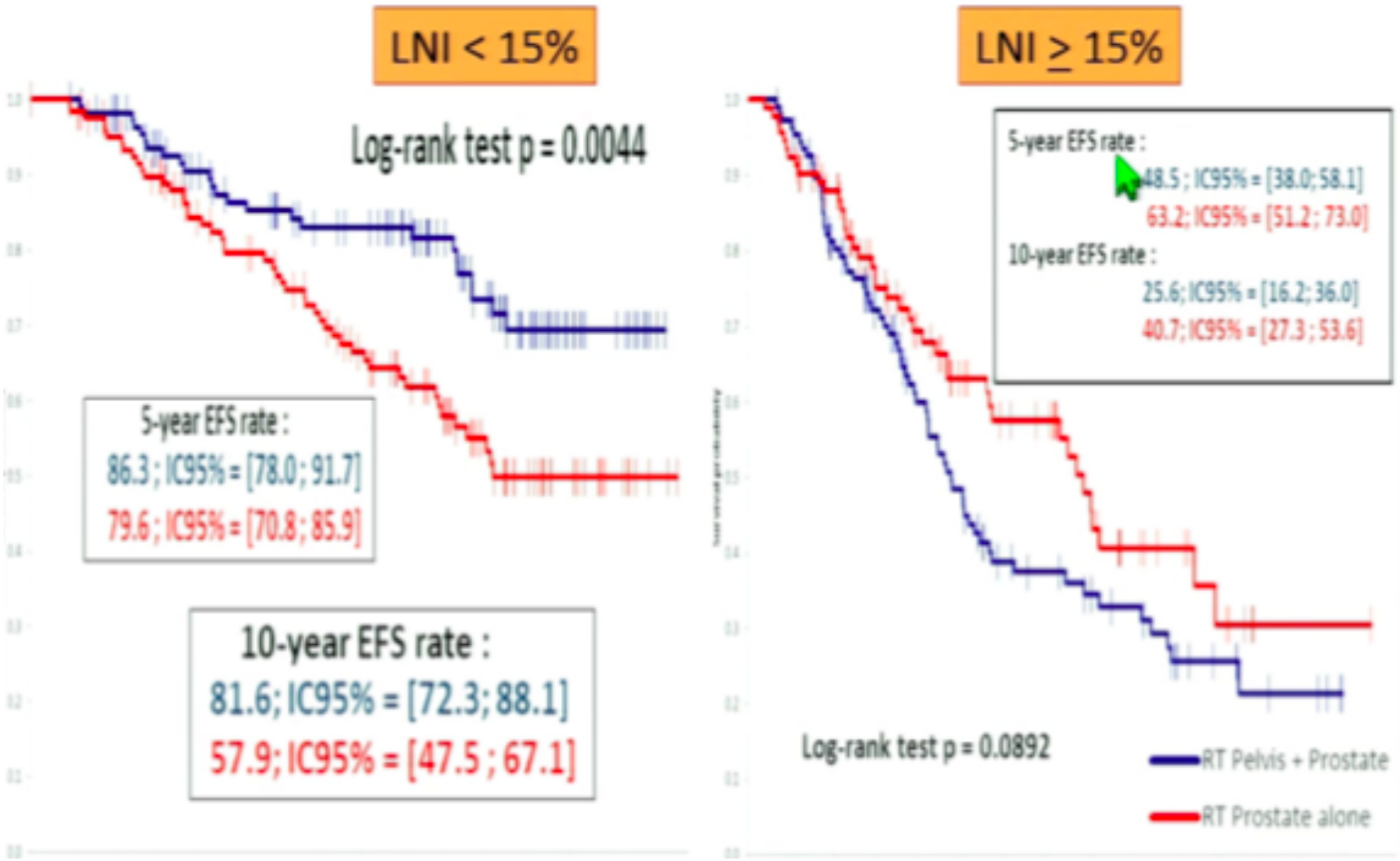


Overall Survival





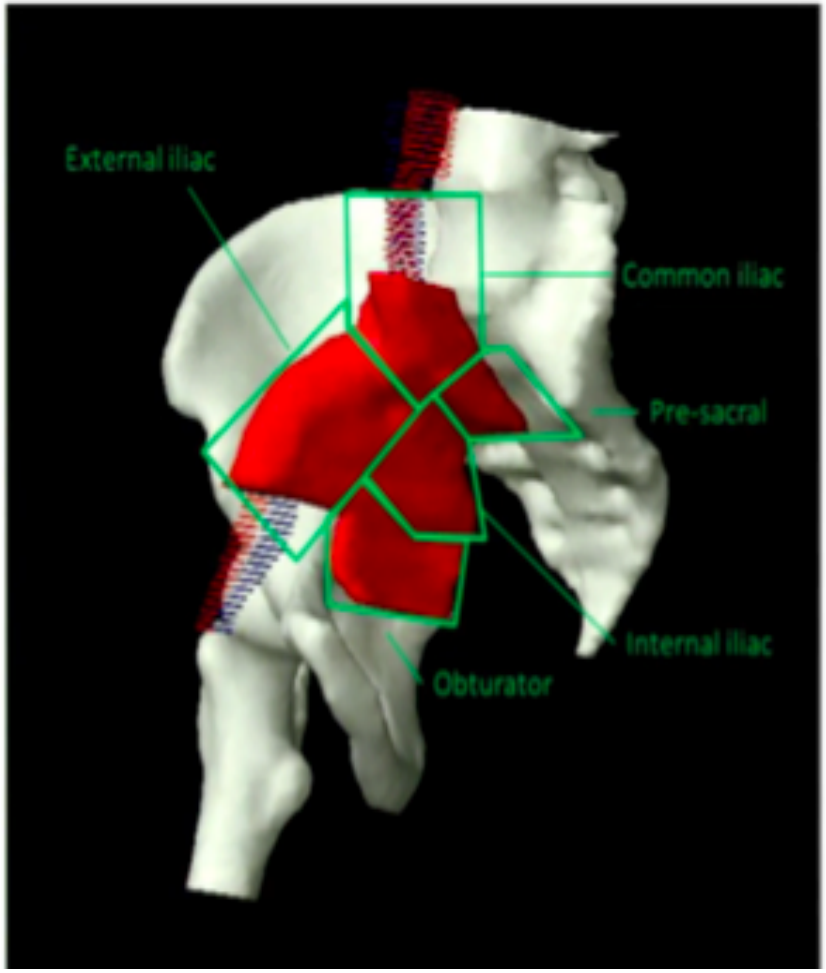
Event Free Survival: according to LNI risk (Roach formula)*



Patterns of Lymph Node Positivity on ^{11}C-acetate PET Imaging in Correlation to the RTOG Pelvic Radiation Field for Prostate Cancer

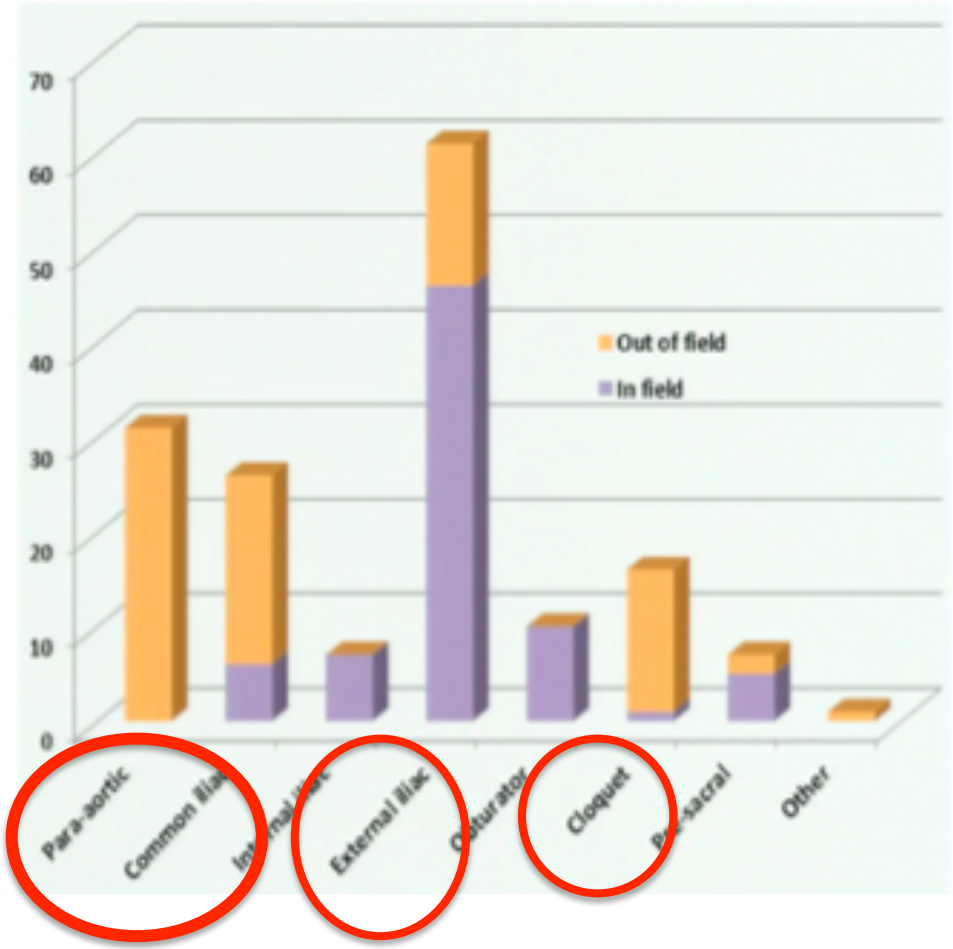
Chris McClinton, MD,* Maryam Niroumand, MD,† Veer Shah, MBChB,† Jacqueline Hill, MPH,† Reginald Dusing, MD,† Parvesh Kumar, MD,* Xinglei Shen, MD*

RTOG Nodal Consensus CTV Contours: High Risk / Locally Advanced Adenocarcinoma of the Prostate

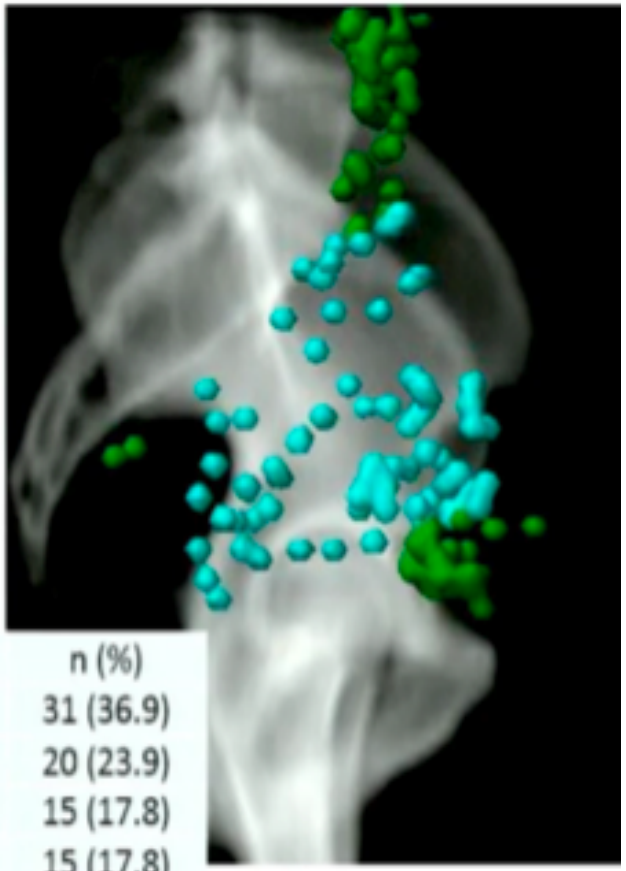


Lymph node distribution

- 159 nodes evaluated
  - 47.2% in-field
  - 52.8% out-of-field
- 78% of patients had at least one out-of-field node



Distribution of out-of-field nodes with standard RTOG field



	n (%)
Para-aortic	31 (36.9)
Common iliac	20 (23.9)
External iliac	15 (17.8)
Cloquet node	15 (17.8)
Internal iliac	0 (0)
Obturator	0 (0)
Pre-sacral	2 (2.4)
Other	1 (1.2)

Conclusion

- Based on ^{11}C-acetate PET, the standard RTOG pelvic radiation field for prostate cancer may miss nearly half of all positive nodes

EUROPEAN UROLOGY 53 (2008) 118–125

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

The Template of the Primary Lymphatic Landing Sites of the Prostate Should Be Revisited: Results of a Multimodality Mapping Study

Agostino Mattei [a], *Frank G. Fuechsel* [b], *Nivedita Bhatta Dhar* [a], *Sebastian H. Warncke* [a], *George N. Thalmann* [a], *Thomas Krause* [b], *Urs E. Studer* [a,*]

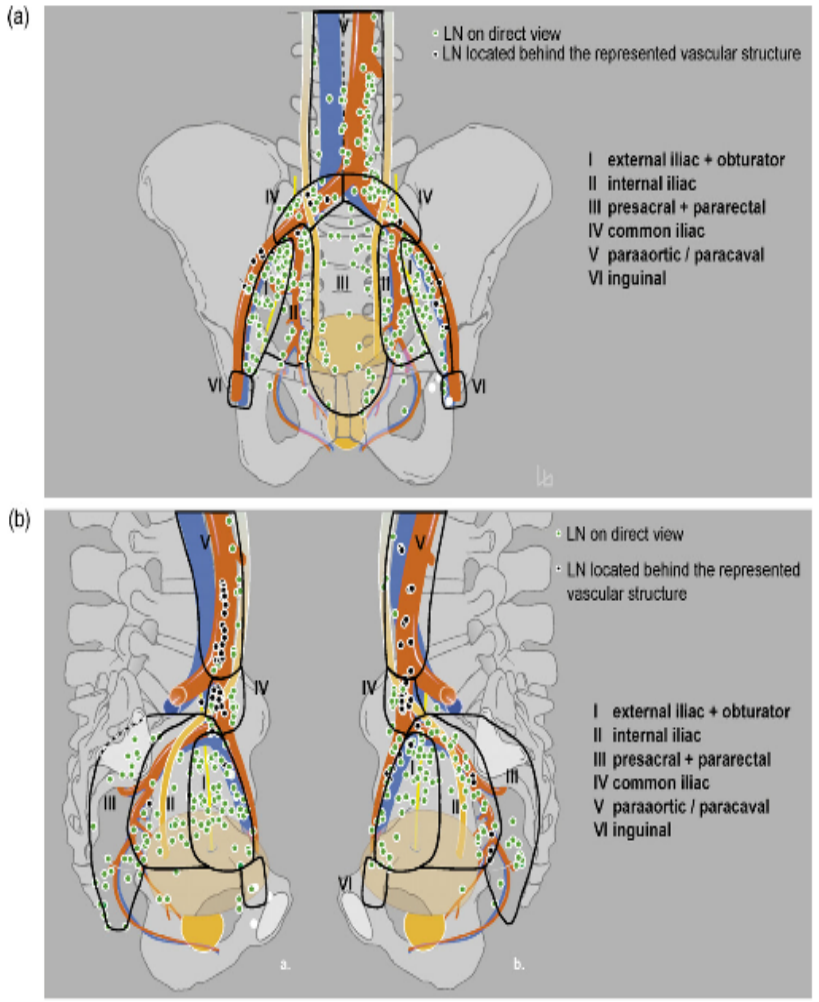


Fig. 2 – Primary lymphatic landing sites of the prostate transferred from 3D datasets and superimposed into idealized anterior-posterior and medio-lateral projection of the pelvis ($n = 317$ for 34 patients). All LNs depicted 3D reconstruction of single-photon emission computed tomography/computed tomography/magnetic resonance imaging (SPECT/CT/MRI) data sets and confirmed by surgery were subsequently transferred into a template projection of the pelvis. LNs are color coded in relation to the vascular structures and ureters. Superimposed are the boundaries of pelvic lymphadenectomy (PLND) subdivided into different regions. (a) Primary lymphatic landing sites of the prostate in anterior-posterior projection of the pelvis. (b) Primary lymphatic landing sites of the prostate in medio-lateral projections of the pelvis. Figs. (b)a. and (b)b. are reconstructions of the left and right hemipelvis, respectively, in the median view and therefore only the LNs of the left and right side are respectively shown.

Pooperacyjna RT układu chłonnego ?

Jeżeli założymy, że stosowana RT w grupie wysokiego ryzyka likwiduje chorobę „mikroskopową“ w układzie chłonnym, to bardzo podobnie (różnica w ognisku pierwotnym) należy traktować pooperacyjną RT po RP kiedy potwierdzono h-pat przerzuty w układzie chłonnym.

Opcja leczenia gdy pN1:

- tylko ADT
- **ADT + RT**, czyli to co realizujemy w przypadku RT bez RP

W ostatnim okresie pojawiły się publikacje wskazujące na:

- możliwość uzyskania zysku z leczenia operacyjnego układu chłonnego.
- możliwość uzyskania zysku z pooperacyjnej WPRT

W grupie wysokiego ryzyka dodanie HT do RT poprawia przeżycia w porównaniu do samodzielnej RT. (RCT level 1)

- Pytanie czy HT działa na komórki raka:
- tylko w sterczu?
- tylko/przede wszystkim w węzłach chłonnych?
- W sterczu i wezłach? Z przewagą w sterczu czy z przewagą w węzłach?

- Po RP z limfadenektomia (pN0) brak zysku z HT. Może dlatego, że efektywność operacji w układzie chłonnym jest wysoka i niepotrzebna „pomoc“ HT.

- Jednak w przypadku pN1 dodanie HT poprawia wyniki.

- zastosowanie dodatkowo uRT WPRT poprawia wyniki leczenia (brak RCT)

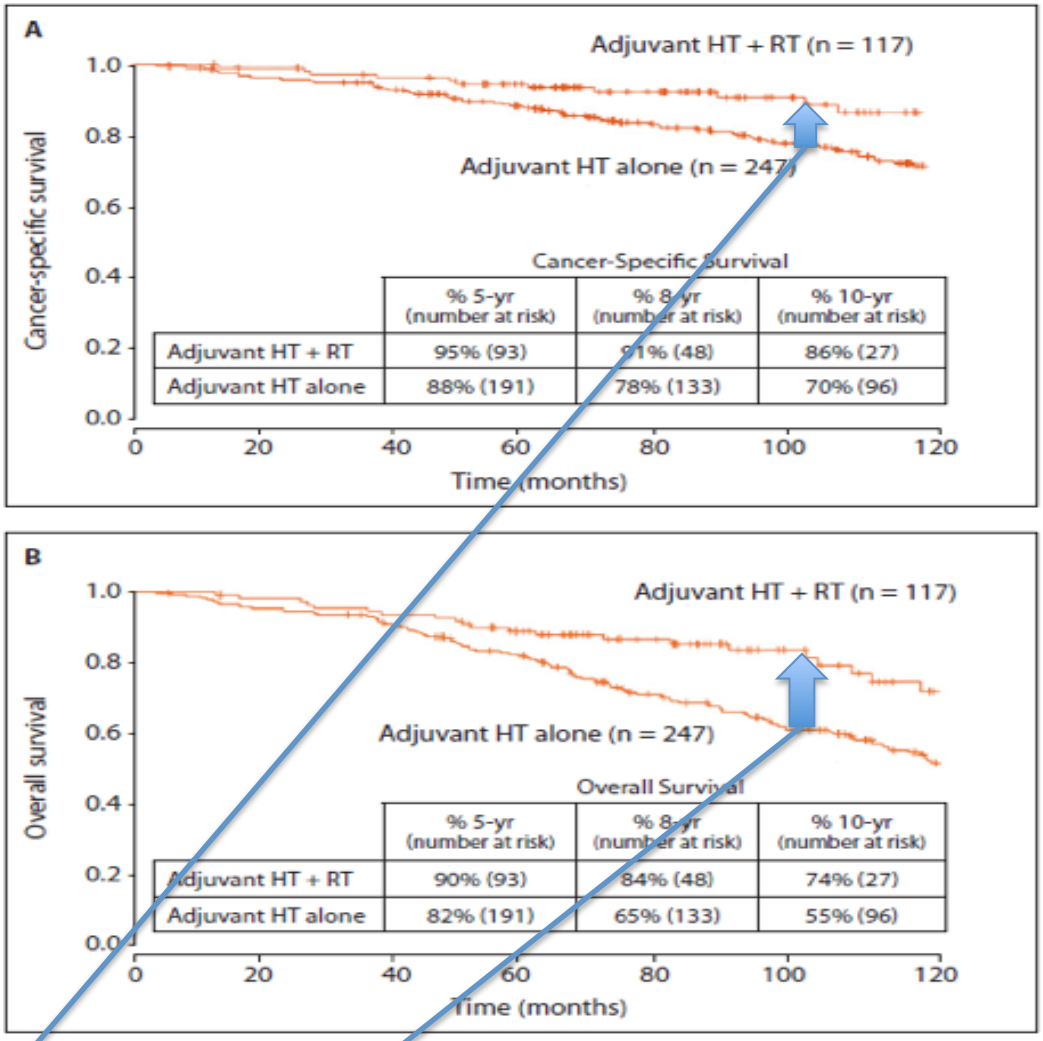


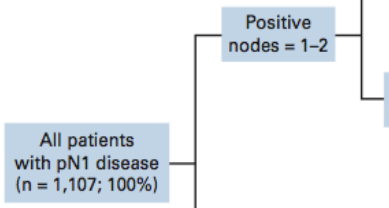
Figure 2: Kaplan-Meier Estimates of Cancer-Specific Survival (A) and Overall Survival (B) After Surgery—according to the type of adjuvant treatment administered (adjuvant radiation therapy [RT] plus hormonal therapy [HT] vs adjuvant HT alone). N = 364. For cancer-specific survival: $P = .004$; hazard ratio (HR) = 2.5. For overall survival: $P < .001$; HR = 2.3. et al. Eur Urol. 2011;59:832-40[27] with permission from Elsevier.

Zysk wynikający z dołączenia WPRT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

Firas Abdollah, R. Jeffrey Karnes, Nazareno Suardi, Cesare Cozzarini, Giorgio Gandaglia, Nicola Fossati, Damiano Vizziello, Maxine Sun, Pierre I. Karakiewicz, Mani Menon, Francesco Montorsi, and Alberto B



Eight-Year CSM-Free Survival (95% CI)

	Entire Cohort	aHT Alone	aRT + aHT	*P*
Gleason score 2–6 (n = 133; 12%)	98.6 (95.8 to 100)	98.4 (95.4 to 100)	100 (100 to 100)	.7
pT2/pT3a and negative SM (n = 131; 11.8%)	96.6 (93.4 to 99.9)	96.8 (93.2 to 100)	96.3 (89.4 to 100)	.4
pT3b/pT4 or positive SM (n = 552; 49.9%)	86.7 (83.0 to 90.6)	84.2 (79.7 to 89.0)	93.1 (87.5 to 99.1)	.03
Positive nodes = 3–4 (n = 160; 14.5%)	85.3 (78.9 to 92.1)	78.8 (69.7 to 89.0)	96.5 (91.8 to 100)	.02
Positive nodes > 4 (n = 131; 11.8%)	72.2 (62.7 to 83.1)	72.0 (60.9 to 85.2)	74.7 (59.2 to 94.3)	.9

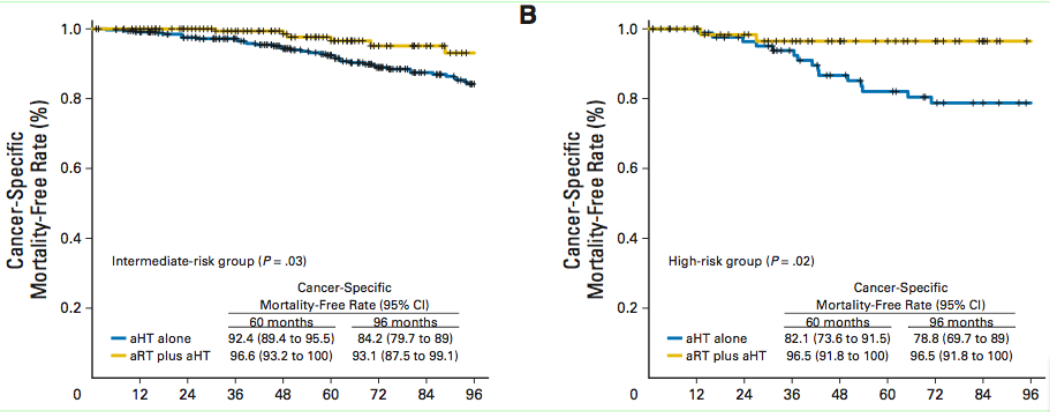


Table 3. Multivariable Cox Regression Analyses Testing the Relationship Between aRT Treatment and Overall Mortality in 1,107 Patients With pN1 PCa Treated With RP, ePLND, and Adjuvant Therapy

	Multivariable Analysis		
Group	HR	95% CI	*P*
Very low risk*	0.01	< 0.01 to > 99.9	.9
Low risk†	0.63	0.22 to 1.82	.4
Intermediate risk‡	0.42	0.25 to 0.70	.001
High risk§	0.32	0.12 to 0.83	.02
Very high risk‖	0.59	0.28 to 1.28	.2

Patients were stratified into risk groups based on regression tree predicting cancer-specific mortality. All multivariable analyses were for age, prostate-specific antigen, pathologic Gleason score, patho-ge, surgical margin, and positive lymph node count.
iations: aRT, adjuvant radiotherapy; ePLND, extended pelvic node dissection; HR, hazard ratio; PCa, prostate cancer; PLN, lymph node; RP, radical prostatectomy.
ow risk: two or fewer PLNs, and Gleason score 2 to 6.
isk: two or fewer PLNs, Gleason score 7 to 10, pT2/pT3a stage, and surgical margins.
ediate risk: two or fewer PLNs, Gleason score 7 to 10, pT3b/pT4 or positive surgical margins.
§High risk: 3 to 4 PLNs.
‖Very high risk: > 4 PLNs.

WPRT po RP

Intermediate risk; 2 lub więcej pLN, GS> 6, pT3b, R1

High risk: 3 – 4 pLNs

Technika RT

- Kolejne etapy RT: (EBRT; P-SV-WPRT + boost BT) – dawka całkowita 45 – 50 Gy
- Kolejne etapy RT: (EBRT; P-SV-WPRT + boost SBRT):

  5 x 5 Gy – WPRT + boost SBRT 3 x 7 Gy

  45 Gy - WPRT + boost SBRT 3 x 7 Gy
- SIB (simultaneous Integrated Boost)
- WPRT
- IGRT?

PLATIN

(Prostate and Lymph Node Irradiation with Integrated-Boost-IMRT)
University of Hidelberg

- irradiation of the pelvic lymph nodes simultaneously with an integrated boost to either the prostate (PLATIN 1),
- the prostate and macroscopic nodes (PLATIN 2),
- the prostate bed (PLATIN 3),
- the prostate bed and macroscopic nodes (PLATIN 4)
- or to macroscopic nodes in patients that had received PBRT before (PLATIN 5).

Helical intensity-modulated Radiotherapy of the Pelvic Lymph Nodes with Integrated Boost to the Prostate Bed - Initial Results of the PLATIN 3 Trial

- Sonja Katayama[1]Email author,
- Gregor Habl[1],
- Kerstin Kessel[1],
- Lutz Edler[2],
- Juergen Debus[1],
- Klaus Herfarth[1] and
- Florian Sterzing[1, 3]

BMC Cancer201414:20

PLATIN 3

Rectum	
Maximum anterior rectal wall	71.4 Gy ± 1.1 Gy
$V_{40\ Gy}$	41.0% ± 13.8% / 41 ml ± 14 ml
$V_{60\ Gy}$	9.5% ± 5.7% / 10 ml ± 6 ml
$V_{70\ Gy}$	1.0% ± 1.5% / 1 ml ± 1 ml
Small bowel	
Maximum	53.1 Gy ± 1.2 Gy
$V_{20\ Gy}$	42.1% ± 15.2% / 672 ml ± 243 ml
$V_{40\ Gy}$	10.3% ± 6.3% / 164 ml ± 101 ml
Bladder	
$V_{40\ Gy}$	40.9% ± 8.9% / 125 ml ± 27 ml
$V_{60\ Gy}$	13.2% ± 8.2% / 40 ml ± 25 ml
$V_{70\ Gy}$	3.5% ± 3.6% / 11 ml ± 11 ml

Publications on acute toxicity of radiotherapy of the prostate bed with or without pelvic irradiation

		Acute grade 1		Acute grade 2		Acute grade 3		Acute grade 4	
		GI	GU	GI	GU	GI	GU	GI	GU
Bellavita et al. [13]	3D-CRT prostate bed 66.6 Gy	48.9% (G1/2)	-	-	-	1.1%	-	0%	0%
Current trial	**IMRT WPRT 51 Gy + boost prostate bed 68 Gy**	**67.5%**	**22.5%**	**22.5%**	**22.5%**	**0%**	**0%**	**0%**	**0%**
Alongi et al.[14]	**IMRT WPRT 50.6 Gy + boost prostate bed 70–72.5 Gy**	-	-	**3.3%**	**6.6%**	**0%**	**0%**	**0%**	**0%**
Deville et al.[15]	**IMRT WPRT 45 Gy Gy + boost prostate bed 70.2 Gy**	**31%**	**67%**	**61%**	**22%**	**0%**	**0%**	**0%**	**0%**
Alongi et al.[14]	*3D-CRT WPRT 50.1 Gy + boost prostate bed 72.1 Gy*	-	-	*8.6%*	*12.3%*	*0%*	*0%*	*0%*	*0%*
Aizer et al.[16]	*3D-CRT WPRT 45 Gy + IMRT boost prostate 75.6 Gy*	*75%*	*44.1%*	*17.6%*	*33.8%*	*1.5%*	*10.3%*	*0%*	*0%*
Roach et al.[4]	*3D-CRT WPRT 45 Gy + boost prostate 70.2 Gy*	-	-	-	-	*2.6% (G3/4)*	*3.9% (G3/4)*	*0%*	*0%*
Liu et al.[17]	*2D WPRT 45 Gy + boost prostate 72 Gy*	*12.2%*	*10.9%*	*1.3%*	*3.8%*	*0.6%*	*0.6%*	*0%*	-

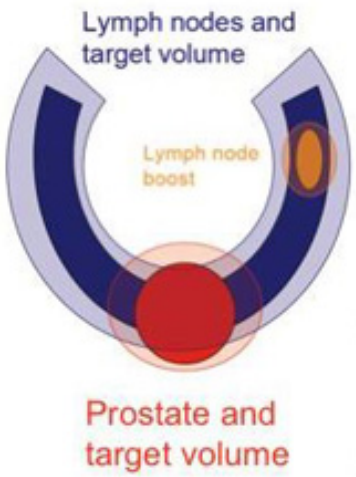
Publications on late toxicity of radiotherapy of the prostate bed with or without pelvic irradiation

		Median follow-up	Late grade 1		Late grade 2		Late grade 3		Late grade 4	
			GI	GU	GI	GU	GI	GU	GI	GU
Bolla et al. [1]	3D-CRT prostate bed 66.0 Gy	60 months	-	-	-	-	4.2%		0%	0%
Bolla et al. [12]	3D-CRT prostate bed 66.0 Gy	127 months	-	-	-	-	5.3%		0%	0%
Wiegel et al. [3]	3D-CRT prostate bed 66.60 Gy	54 months	-	-	1.4%	2.0%	-	0.5%	0%	0%
Bellavita et al. [13]	3D-CRT prostate bed 66.6 Gy	56 months	7.1% (G1/2)	9.9% (G1/2)	-	-	0.5%	5.5%	0%	0%
Ost et al. [18]	IMRT/3D-CRT prostate bed 69.1 Gy	60 months	~ 28%	~ 34%	~ 5%	~ 17%	< 1%	10%	0%	0%
Current trial	**IMRT WPRT 51 Gy + boost prostate bed 68 Gy**	**24 months**	**7.5%**	**22.5%**	**10.0%**	**5.0%**	**5.0%**	**0%**	**0%**	**0%**
Deville et al.[15]	**IMRT WPRT 45 Gy Gy + boost prostate bed 70.2 Gy**	**26 months**	**11%**	**50%**	**3%**	**17%**	**0%**	**11%**	**0%**	**0%**
Aizer et al.[16]	*3D-CRT WPRT 45 Gy + IMRT boost prostate 75.6 Gy*	*30 months*	*2.9%*	*1.5%*	*4.4%*	*1.5%*	*1.5%*	*0%*	*0%*	*0%*
Roach et al.[4]	*3D-CRT WPRT 45 Gy + boost prostate 70.2 Gy*	-	-	-	-	-	*4.3% (G3/4)*	*3.0% (G3/4)*	-	-

Pelvic Lymph Node Irradiation for prostate cancer

The role of pelvic lymph-node irradiation in prostate cancer remains controversial particularly following the recent results of two phase III trials. Nevertheless it is argued that for 'high-risk' disease standard therapy should remain prostate and pelvic radiotherapy with three years of androgen suppression, as this has been the treatment used in phase III trials assessing the duration of hormonal therapy. In the UK there is some reluctance to using pelvic irradiation due to the risk of acute and late bowel morbidity.

We have completed recruitment (N= 206) to a dose-escalation study using IMRT to deliver doses of 50Gy, 55Gy, and 60Gy to pelvic lymph nodes in sequential cohorts of patients. Toxicity in the first two cohorts is low (Grade 2, 8.8%) and related to bowel volume treated. Late side-effect data (follow-up 1-4 years) from the 60Gy pelvic dose group (N=124) Shows a Grade 2 toxicity rate of 12% and we will refine dose volume constraints. A further hypofractionated cohort (N=124) using a four to five week schedule completed recruitment during 2010 and recruitment for patients with radiologically positive LN is ongoing.



Prostate dose/ fractions/weeks	Lymph node dose			LN boost
	LEVEL 1	LEVEL2	LEVEL3	
70Gy/35F/7.5w 2 Gy fractions	50Gy	55Gy	60Gy	5Gy
60/20F/4w 3 Gy fractions		47Gy		4Gy

Ruchomość stercza

- Ruchomość stercza - 1 cm – jeżeli skoncentrujemy – skorygujemy geometrię wg stercza to wówczas układ chłonny otrzyma dawkę mniejszą o około 15 % aniżeli przewidziano

Med Phys. 2012 Feb;39(2):1119-24. doi: 10.1118/1.3679859.

Irradiation of the prostate and pelvic lymph nodes with an adaptive algorithm.

Hwang AB[1], Chen J, Nguyen TB, Gottschalk AG, Roach MR, Pouliot J.

Toksyczność WPRT ?

MSKCC

	2D,	**3DCRT,**	**IMRT**
• Dawka jelito V45;	41,7%	22,6%	9,1%
• Rectum mean D;	40,4 Gy	37,3 Gy	27,3 Gy
• Bladder V45;	87,2%	56,8%	25,6%

- CHUNG et al.

	IMRT	**v.**	**IMRT-IGRT**
• Rectal Grade 2	80%		13%
• Bladder	60%		13%
• No grade 3-5			

J Clin Oncol. 2007 Dec 1;25(34):5366-73.

Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01.

Pommier P[1], Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le Prise E, Wagner JP, Hay MH, Beckendorf V, Suchaud JP, Pabot du Chatelard PM, Bernier V, Voirin N, Perol D, Carrie C.

Author information

Abstract

PURPOSE: To assess the benefit and toxicity and quality-of-life (QOL) outcomes of pelvic nodes irradiation in nonmetastatic prostate carcinoma patients.

PATIENTS AND METHODS: Between December 1998 and June 2004, 444 patients with T1b-T3, N0 pNx, M0 prostate carcinoma were randomly assigned to either pelvic and prostate radiotherapy or prostate radiotherapy only. Patients were stratified according to the prognostic factor of lymph node involvement (LNI). Short-term 6-month neoadjuvant and concomitant hormonal therapy was allowed only for patients in the high-risk group. The pelvic dose was 46 Gy. The total dose recommended to the prostate was changed during the course of the study from 66 Gy to 70 Gy. Criteria for progression-free survival (PFS) included biologic prostate-specific antigen recurrences or a local or metastatic evolution. Acute and late toxicities were recorded according to the Radiation Therapy Oncology Group and Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scales, respectively. The QOL outcome was recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, the International Prostatic Symptom Score, and the Sexual Function Index scales.

RESULTS: With a 42.1-month median follow-up time, the 5-year PFS and overall survival were similar in the two treatment arms for the whole series and for each stratified group. On multivariate analysis, low LNI risk and hormonal therapy were statistically associated with increased PFS. However, subgroup analyses based on these factors did not show any benefit for pelvic irradiation. There were no significant differences in acute and late digestive toxicities and in QOL outcomes.

CONCLUSION: Pelvic node irradiation was well tolerated but did not improve PFS.

Br J Radiol. 2016 Jul;89(1063):20150985. doi: 10.1259/bjr.20150985. Epub 2016 Apr 25.

No increase in toxicity of pelvic irradiation when intensity modulation is employed: clinical and dosimetric data of 208 patients treated with post-prostatectomy radiotherapy.

Jereczek-Fossa BA[1,2], Ciardo D[1], Ferrario S[1,2], Fossati P[1,2], Fanetti G[1,2], Zerini D[1], Zannoni D[3], Fodor C[1], Gerardi MA[1,2], Surgo A[1,2], Muto M[1,2], Cambria R[4], De Cobelli O[2,5], Orecchia R[1,2].

Int J Radiat Oncol Biol Phys. 2010 Nov 1;78(3):763-72. doi: 10.1016/j.ijrobp.2009.08.043. Epub 2010 Feb 18.

Clinical toxicities and dosimetric parameters after whole-pelvis versus prostate-only intensity-modulated radiation therapy for prostate cancer.

Deville C[1], Both S, Hwang WT, Tochner Z, Vapiwala N.

CONCLUSIONS: Despite dosimetric differences in the volume of bowel, bladder, and rectum irradiated in the low-dose and median-dose regions, WP IMRT results only in a clinically significant increase in acute GI toxicity, in comparison to PO IMRT, with no difference in GU or late GI toxicity.

Hematologic Toxicity in Patients Treated With Postprostatectomy Whole-Pelvis Irradiation With Different Intensity Modulated Radiation Therapy Techniques Is Not Negligible and Is Prolonged: Preliminary Results of a Longitudinal, Observational Study

Cesare Cozzarini, MD, Barbara Noris Chiorda, MD, Carla Sini, PhD, Claudio Fiorino, PhD, Alberto Briganti, MD, Francesco Montorsi, MD, Nadia Di Muzio, MD

Methods and Materials

This analysis pertains to 125 patients (70 from a pilot study and 55 from an observational protocol) for whom 1 baseline and at least 3 subsequent blood samples (median 6), obtained at irradiation midpoint and end, and thereafter at 3, 6, and 12 months, were available. Patients were treated with adjuvant (n=73) or salvage intent; static-field IMRT (n=19); volumetric modulated arc therapy (n=60) or helical Tomotherapy (n=46); and conventional (n=39) or moderately hypofractionated (median 2.35 Gy per fraction, n=86) regimens. The median 2-Gy equivalent dose (EQD2) to the prostatic bed was 70.4 Gy with a lymph-nodal planning target volume of 50.2 Gy. Clinical and dosimetric data were collected.

Results

Both leukopenia and thrombocytopenia were significant (median nadir count 65% and 67% of baseline, respectively), with leukopenia also persisting (1-year median count 75% of baseline). Lymphopenia was the major contributor to the severity and 1-year persistence of leukopenia; all patients developed acute grade ≥1 lymphopenia (61% and 26% grade 2 and ≥3, respectively), whereas 1-year grade ≥2 lymphopenia was still present in 16%. In addition to an independent predictive role of corresponding baseline values, multivariable analyses highlighted that higher EQD2 doses to lymph nodal planning target volume increased risk of acute neutropenia and hypofractionation for acute thrombocytopenia. Of note, patients of older age were at higher risk for acute grade 2 lymphopenia, and interestingly, increased risk of grade >2 lymphopenia for those who smoked at least one year. No role for different IMRT techniques indicated.

Conclusions

Leukopenia and lymphopenia after postprostatectomy WPRT were found to be less negligible and more prolonged than expected. A number of radiation-related and clinical factors favoring hematologic toxicity, whose awareness may be crucial when prescribing WPRT, in particular if concomitant to chemotherapy, were identified.

Impact of Proton Therapy to the Prostate Alone versus Whole Pelvis on Patient Reported Outcomes and Toxicities in High Risk Prostate Cancer Patients

Lisa A. McGee, Bradford S. Hoppe, Randal H Henderson, Christopher G. Morris, R. C. Nichols, Jr., Zhong Su, Zheng Li, William M. Mendenhall, Williams CR, Mendenhall NP

University of Florida Proton Therapy Institute, Jacksonville, Florida

Purpose

- Investigate quality of life (QOL) outcomes and gastrointestinal (GI) toxicity in men with high-risk prostate cancer undergoing definitive prostate-only proton therapy (POPT) v. whole-pelvis radiotherapy (WPRT)

Methods and Materials

- 192 men with high-risk prostate cancer were treated with definitive POPT (n=149) or WPRT (n=43) from 2006-11
- WPRT: delivered using photon-based IMRT followed by proton boost to the prostate
- Indications for WPRT:
  - ≥ 15% risk of node involvement per MSKCC prostate cancer nomogram (n=40)
  - Node-positive disease (n=3)
- Men receiving WPRT were more likely to have received androgen deprivation therapy (70% v. 56%)
- Toxicity was assessed per CTCAE v3.0 weekly during treatment and every 6 months thereafter.
- Expanded Prostate Cancer Index Composite (EPIC) questionnaires were collected at baseline and every 6 months

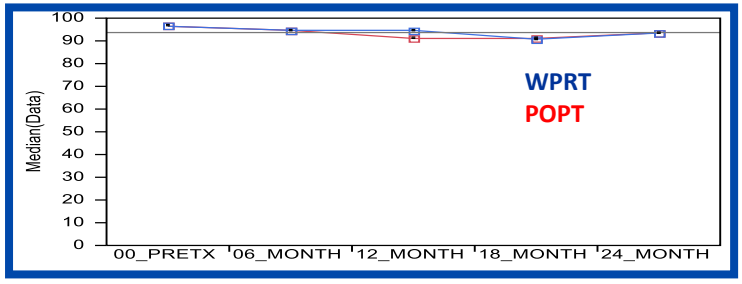
Results

- Median follow-up: 2 years
- Two-year freedom from biochemical failure: 67% WPRT v. 89% for POPT (p=0.046)
- No difference in 2-year overall survival: 95% WPRT v. 98% POPT
- No significant differences for bowel-related QOL, including bowel summary after 6 (94.6 WPRT v. 94.6 POPT), 12 (94.6 WPRT v. 91.1 POPT), or 24 (93.5 WPRT v. 93.5 POPT) months of follow up or for bowel function or bowel bother
- No patient experienced a grade 3+ GI toxicity
- Acute grade 2 GI toxicities occurred in 12% of WPRT patients v. 1% of POPT patients (p=0.002) and were due to patients receiving hydrocortisone (HC) suppositories
- Late grade 2 GI toxicities occurred in 7% of the WPRT patients versus 15% of the POPT patients (p=0.139)
  - 7 POPT and 2 WPRT patients required formalin or other minor cautery
  - 15 POPT and 0 WPRT patients required HC suppositories
  - 1 WPRT patient experienced grade 2 proctitis
  - 1 POPT patient experienced grade 2 incontinence

Patient Characteristics	POPT	WPRT
Total Patients (n)	149	43
Age: ≥ 60 < 60	89% 11%	77% 23%
Stage: T1-T2 T3-T4 N1	98% 2% 0%	81% 19% 7%
Gleason Score: 6-7 ≥8	16% 84%	23% 77%
Pre-treatment PSA: <10 10--<20 ≥20	70% 14% 16%	25% 26% 49%

Predictors of grade 2 GI Toxicity	P value
Age ≥ 70	0.0336
Total Dose > 79.2 CGE	0.0331
Pre-treatment statin use	0.028
Blood thinner use at treatment start	0.0173

No Difference in Bowel-Related Quality of Life



Median EPIC bowel summary subscores graphed over time

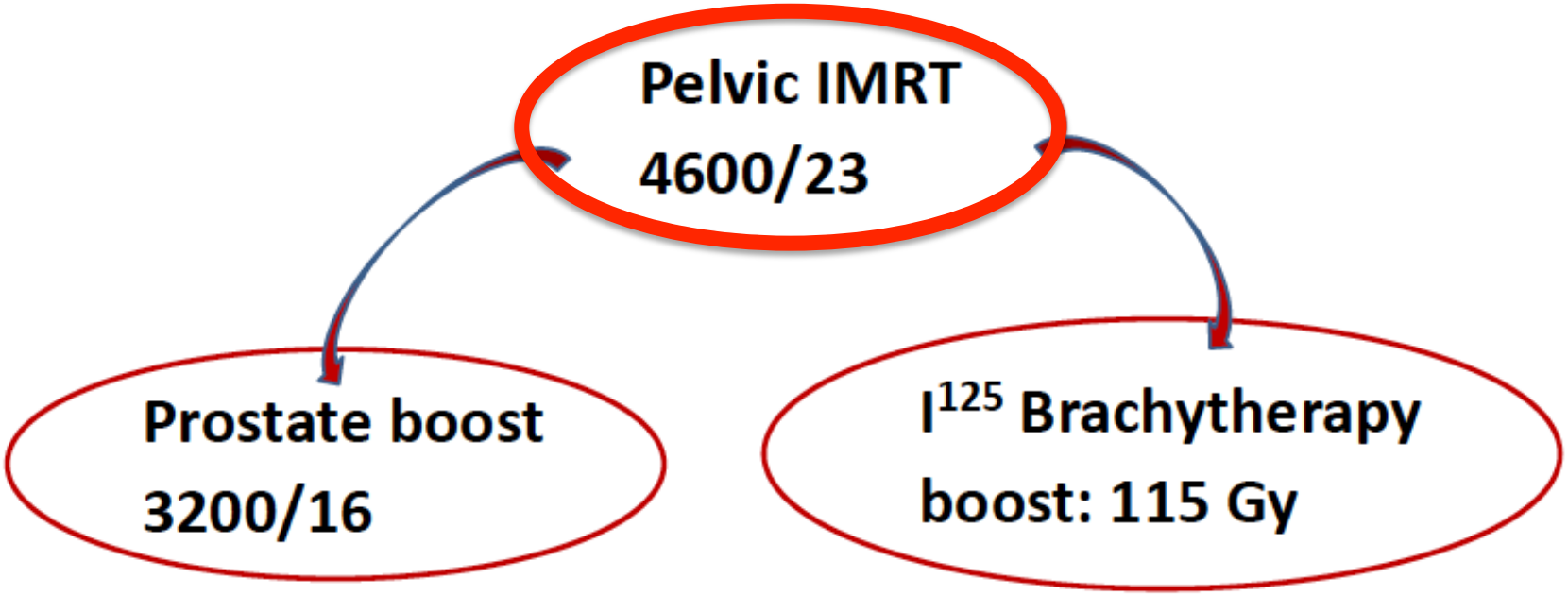
Conclusions

- WPRT resulted in higher acute grade 2 GI toxicity than POPT
- However, WPRT did not result in worse EPIC bowel summary, bowel function, or bowel bother at 6, 12, or 24 months and there was no difference in late GI toxicity
- Longer follow-up is needed

Corresponding author: Bradford S. Hoppe, bhoppe@floridaproton.org

Canadian ASCENDE-RT *WJ Morris et al IJROBP 2016*

- Phase 3: 78 Gy vs. 46 Gy + LDR Brachytherapy
- n=398: follow up 5-11 years
  - High risk and high tier intermediate risk
  - 1 year ADT (8 month neoadj + 4 month concurrent/adjuvant)



N+

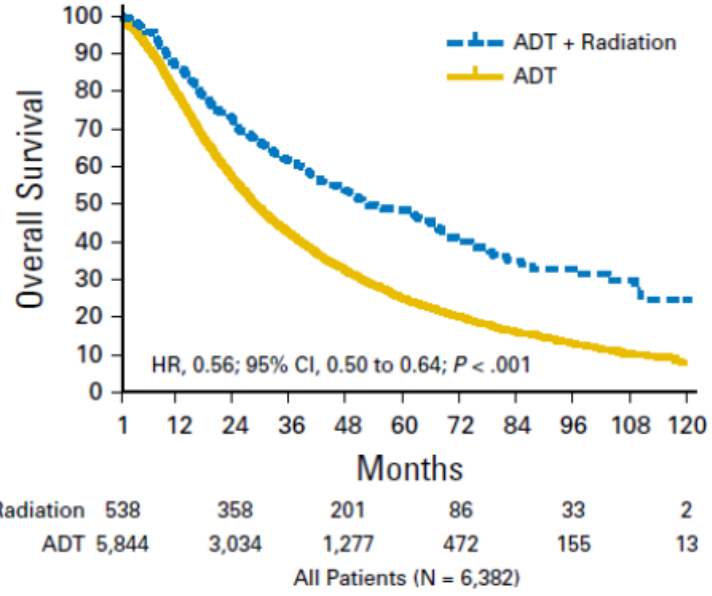
Improved Survival With Prostate Radiation in Addition to ADT for Men With Newly Diagnosed Metastatic Prostate Cancer.
Rusthoven CG et al., J Clin Oncol 2016; 34: 2835 - 2842

- National Cancer Database 2004 - 2012: mPCA treated with ADT with w/o RT
- n = 6382 pts of whom 538 (8.4%) received RT
  - n = 5844 (91.6%) with ADT alone
  - n = 538 (8.4%) with ADT and RT
- median follow-up 5.1 years

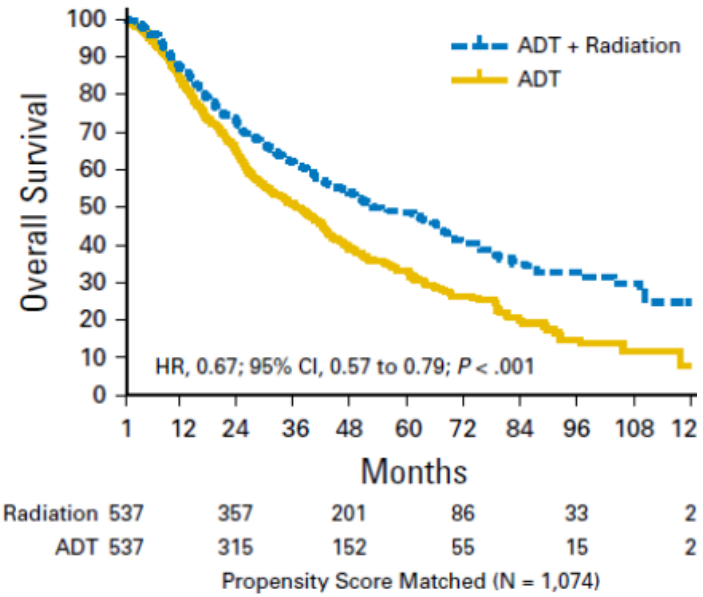
Improved Survival With Prostate Radiation in Addition to ADT for Men With Newly Diagnosed Metastatic Prostate Cancer.

Rusthoven CG et al., J Clin Oncol 2016; 34: 2835 - 2842

A



B



Efficacy of local treatment in patients with prostate cancer with clinically pelvic lymph node-positive disease at initial diagnosis. Fossati N et al., GU ASCO 2017

Methods:

National Cancer Data Base (2004-2012): 2,967 individuals with LT+/-ADT vs. ADT alone for cN1 PCa.

Results:

1,987 (67.0%) and 980 (33.0%) patients received LT+/-ADT and ADT alone

LT+/-ADT group: 751 (37.8%) RP/ADT and 1,236 (62.2%) RT+/-ADT

LT+/-ADT was associated with a significant overall mortality-free survival benefit (HR = 0.31; 95% CI = [0.13-0.74]; *P*= 0.007)

ADT + LT

At 5-year, **overall mortality-free survival** wa **78.8%** (95% CI: 74.1%-83.9%) vs **49.2%** (95% CI: 33.9%-71.4%) in the LT+/-ADT vs. ADT alone

ADT

Androgen Deprivation With or Without Radiation Therapy for Clinically Node-Positive Prostate Cancer.

Lin CC et al., J Natl Cancer Inst 2015: 107: djv 119

A

Full sample selection schema

Patients, age 18 to 90 years, diagnosed during 2004-2011 with first primary invasive malignant clinically node-positive prostate cancer (ICD-O-3: C61.9) without the presence of distant metastasis who did not undergo radical prostatectomy (n = 3744)

Exclusions:

Patients with missing information in

- cancer diagnosis date (n = 13)
- treatment (n = 21)
- census region (n = 23)
- insurance (n = 109)

Government sponsored insurance other than Medicaid or Medicare (n = 38)

Analytic study population (n = 3540)

ADT alone: 1141
ADT+RT: 1818
RT alone: 220
No ADT/No RT: 361

B

Survival analyses cohort and propensity score matching flow chart

Patients who were treated with ADT alone (n = 388) or ADT+RT (n = 595) and diagnosed between 2004 and 2006.

Estimated Propensity Score Model

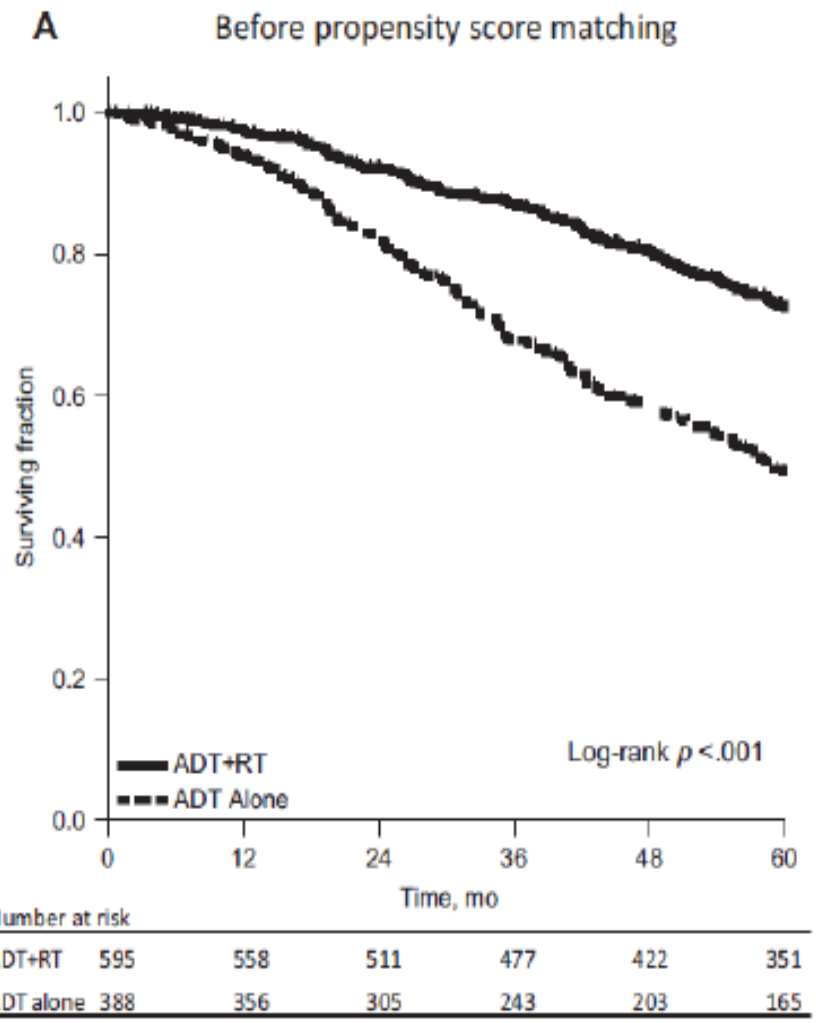
The probability of being treated with ADT+RT was estimated using multivariable logistic regression with all variables listed in Table 2 for the cohort of 983 patients.

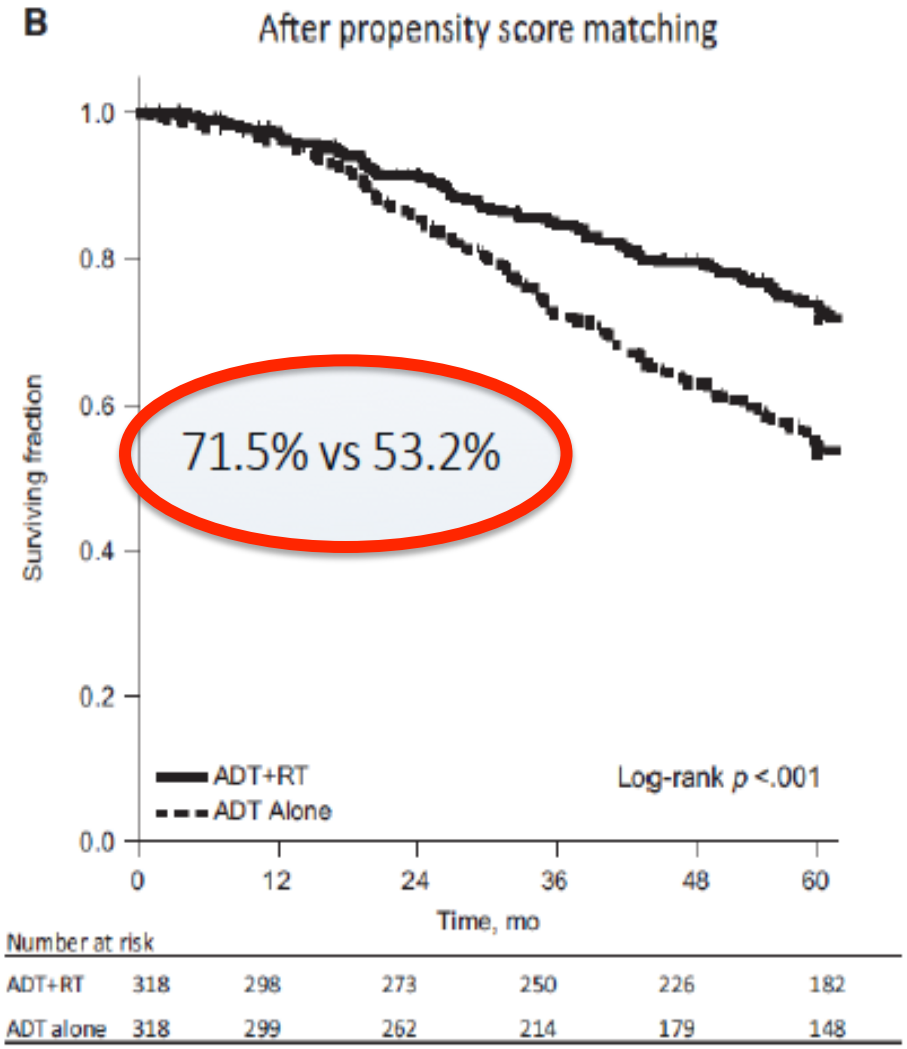
Propensity Score Matching

Patients treated with ADT alone were matched to patients treated with ADT+RT who had the closest propensity score (1:1 match) by a greedy 5 to 1 digit matching algorithm. Patients treated with ADT alone who did not have a match to a patient treated with ADT+RT were excluded.

Matched Sample

The final matched sample consisted of 318 patients treated with ADT alone and 318 patients treated with ADT+RT.


A
Before propensity score matching
1.0
0.8
0.6
0.4
0.2
0.0
Surviving fraction
ADT+RT
ADT Alone
Log-rank p <.001
0
12
24
36
48
60
Time, mo
Number at risk
ADT+RT 595 558 511 477 422 351
ADT alone 388 356 305 243 203 165


B
After propensity score matching
1.0
0.8
0.6
0.4
0.2
0.0
Surviving fraction
71.5% vs 53.2%
ADT+RT
ADT Alone
Log-rank p <.001
0
12
24
36
48
60
Time, mo
Number at risk
ADT+RT 318 298 273 250 226 182
ADT alone 318 299 262 214 179 148

cN1 (> 1 cm)
STAMPEDE Arm A
badanie nie randomizowane

- ADT + WPRT (46-50 Gy) - RT (74 Gy) 71 chorych
- ADT bez WPRT 86 chorych

2 letnie PFS

- 89% gdy WPRT
- 64% bez WPRT

RT ratująca

Clin Genitourin Cancer. 2015 Aug;13(4):e279-84. doi: 10.1016/j.clgc.2014.12.014. Epub 2014 Dec 30.

Salvage Stereotactic Body Radiotherapy for Patients With Prostate Cancer With Isolated Lymph Node Metastasis: A Single-Center Experience.

Ponti E[1], Ingrosso G[2], Carosi A[1], Di Murro L[1], Lancia A[1], Pietrasanta F[1], Santoni R[1].

- 16 chorych z przerzutem do układu chłonnego
- SBRT +/- ADT (50% chorych)
- 1 x 12 Gy,
- 5 x 7 Gy = 35 Gy
- Efektywność miejscowa 94%

Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):889-97. doi: 10.1016/j.ijrobp.2010.11.031. Epub 2011 Jan 27.

Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer.

Jereczek-Fossa BA[1], Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, Zerini D, Gherardi F, Ascione C, Bossi-Zanetti I, Mauro R, Bregantin A, Bianchi LC, De Cobelli O, Orecchia R.

- 34 chorych z tego 16 cN1
- SBRT 5 x 6 Gy = 30 Gy

Na co czekamy ?

RTOG 0924

NRG ONCOLOGY

RTOG 0924

ANDROGEN DEPRIVATION THERAPY AND HIGH DOSE RADIOTHERAPY WITH OR WITHOUT WHOLE-PELVIC RADIOTHERAPY IN UNFAVORABLE INTERMEDIATE OR FAVORABLE HIGH RISK PROSTATE CANCER: A PHASE III RANDOMIZED TRIAL

STRATIFY		RANDOMIZE	
	Risk Group 1. GS 7-10 + T1c-T2b + PSA < 50 ng/ml 2. GS 6 + T2c-T4 or ≥ 50% biopsies + PSA < 50 ng/ml 3. GS 6 + T1c-T2b + PSA > 20 ng/ml		**Arm 1:** Neoadjuvant androgen deprivation therapy + prostate & seminal vesicle RT + boost to prostate & proximal seminal vesicles
	Type of RT Boost 1. IMRT 2. Brachytherapy (LDR using PPI or HDR)		**Arm 2:** Neoadjuvant Androgen Deprivation Therapy + whole-pelvic RT + boost to prostate & proximal seminal vesicles
	Duration of Androgen Deprivation Therapy 1. Short Term (6 months) 2. Long Term (32 months)*		

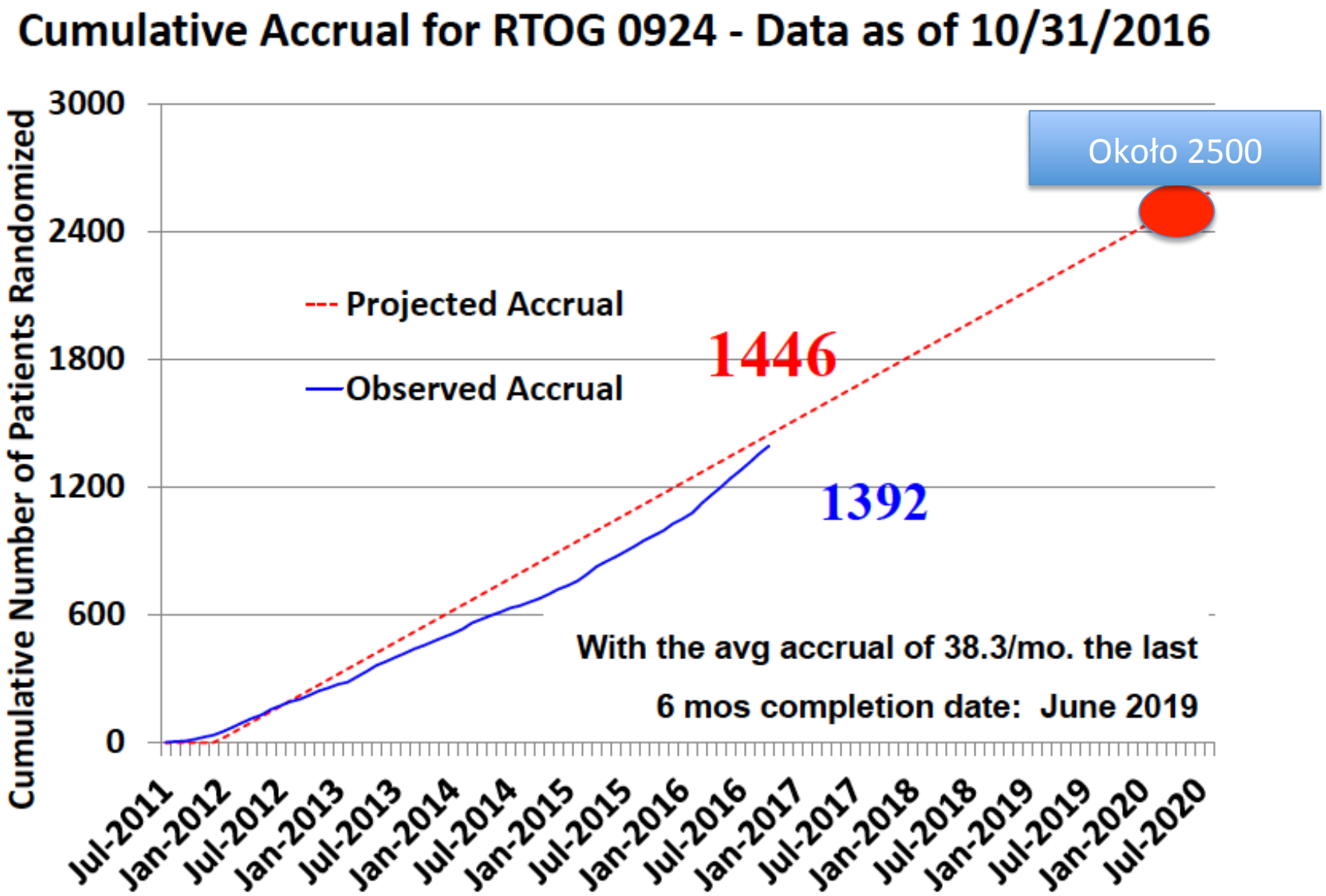
* 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = avg 32 months

Patient Population: (See Section 3.0 for Eligibility) (2/26/14)
Patients who are most likely to benefit from androgen deprivation therapy and whole-pelvic radiotherapy, defined as:

a) Having a significant risk of lymph node involvement (e.g. >15%, based on the Roach formula);
b) Being in one of the following risk groups:
   - GS 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk patients);
   - GS 6 + T2c-T4 (palpation) + PSA < 50 ng/ml **OR** Gleason score 6 + ≥ 50% biopsies + PSA < 50 ng/ml;
   - GS 6 + T1c-T2b (palpation) + PSA > 20 ng/ml.

Required Sample Size: **2,580 patients**

RTOG 0924 rekrutacja chorych

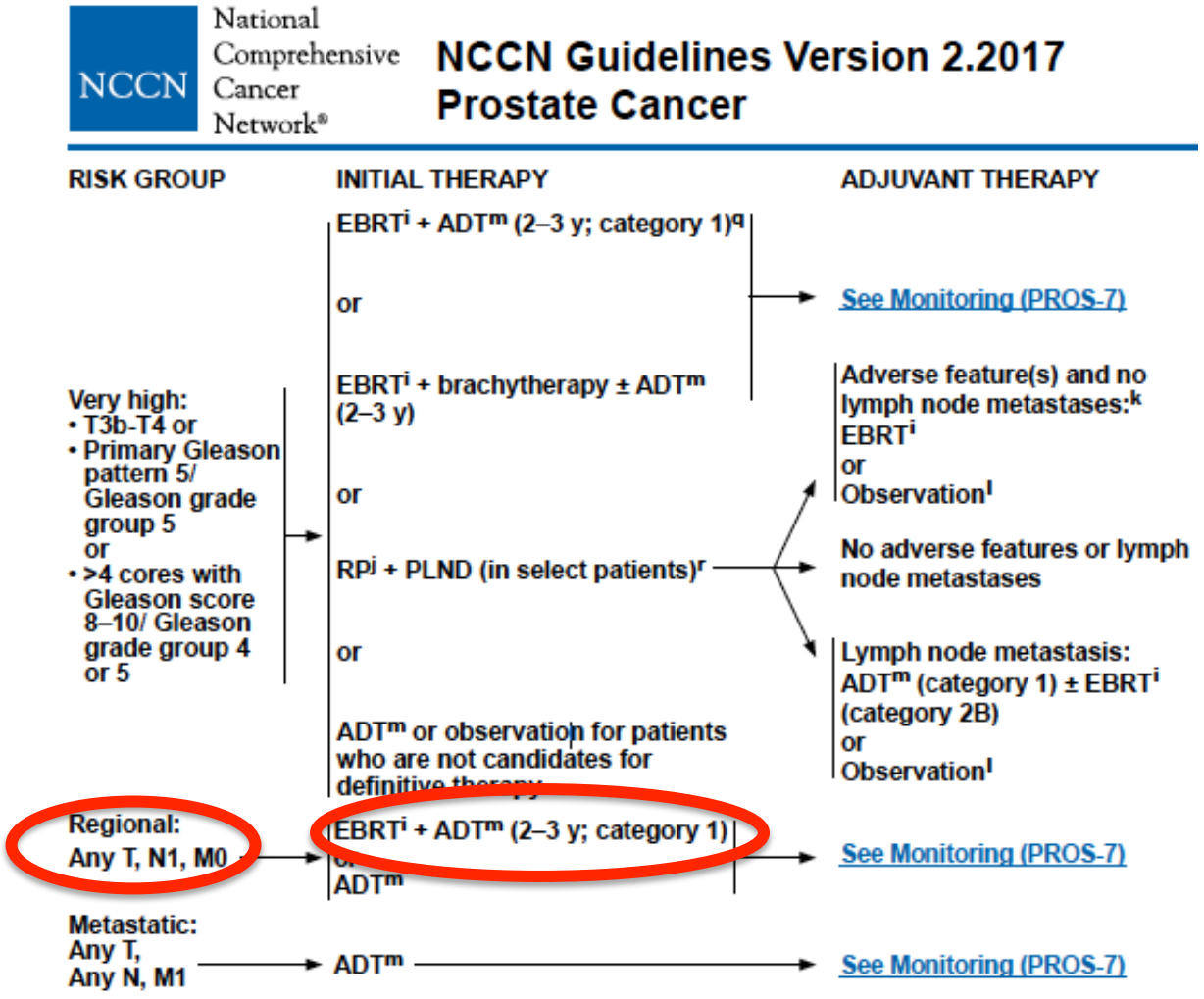


N0 – wysokie & bardzo wysokie ryzyko

ADT + WPRT + eskalacja dawki Stercz

- Praktycznie we wszystkich RCT (ADT + RT) w grupie high-risk stosowano WPRT; czyli odtwarzam warunki badań klinicznych.
- Więcej jest analiz retrospektywnych, które wskazują na zysk z WPRT aniżeli jego brak, również własna.
- RCT które pokazały brak zysku dla WPRT miały istotne wady; istotny błąd geograficzny, dawka RT, zły dobór chorych.
- Bardzo dobra tolerancja WPRT w materiale własnym i danych z publikacji.
- W RP leczenie układu chłonnego jest standardem postępowania; leczymy ten sam nowotwór ale strategia inna?

- Jako onkolog; jeżeli okaże się – a w to wierzę, że dobrze zaprojektowane RCT wykaże zysk z WPRT, to będę mógł powiedzieć, że optymalnie leczyłem dużą grupę chorych.

N+

- Dotychczas nie leczony – leczymy radykalnie (ADT + RT)
- Po leczeniu – indywidualizacja postępowania – zwykle SBRT +/- ADT