Localised High Risk Prostate Cancer: Oncological and functional outcomes (PSA +20ng/ml; Gleason:8-10; T2c+) Radical Surgery

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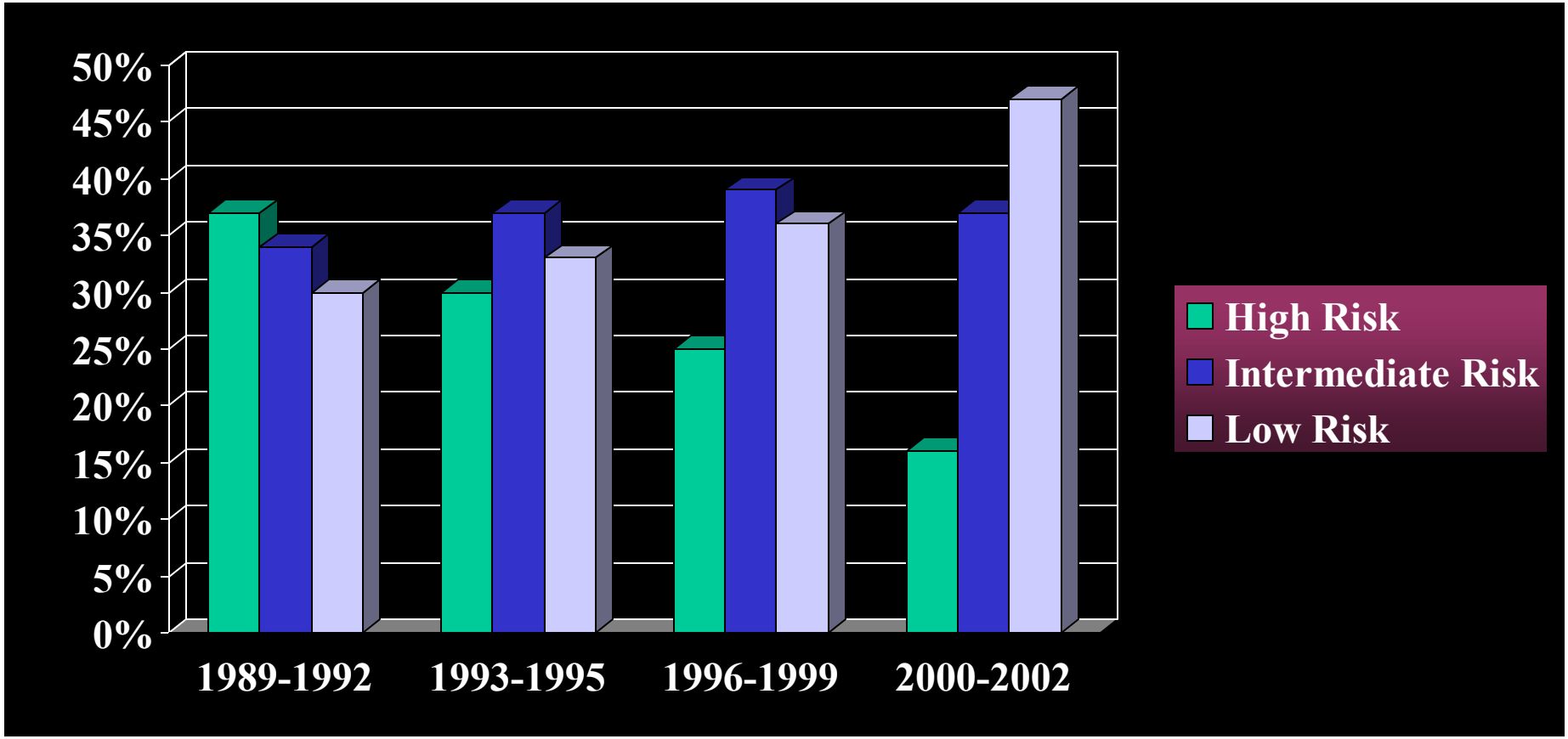
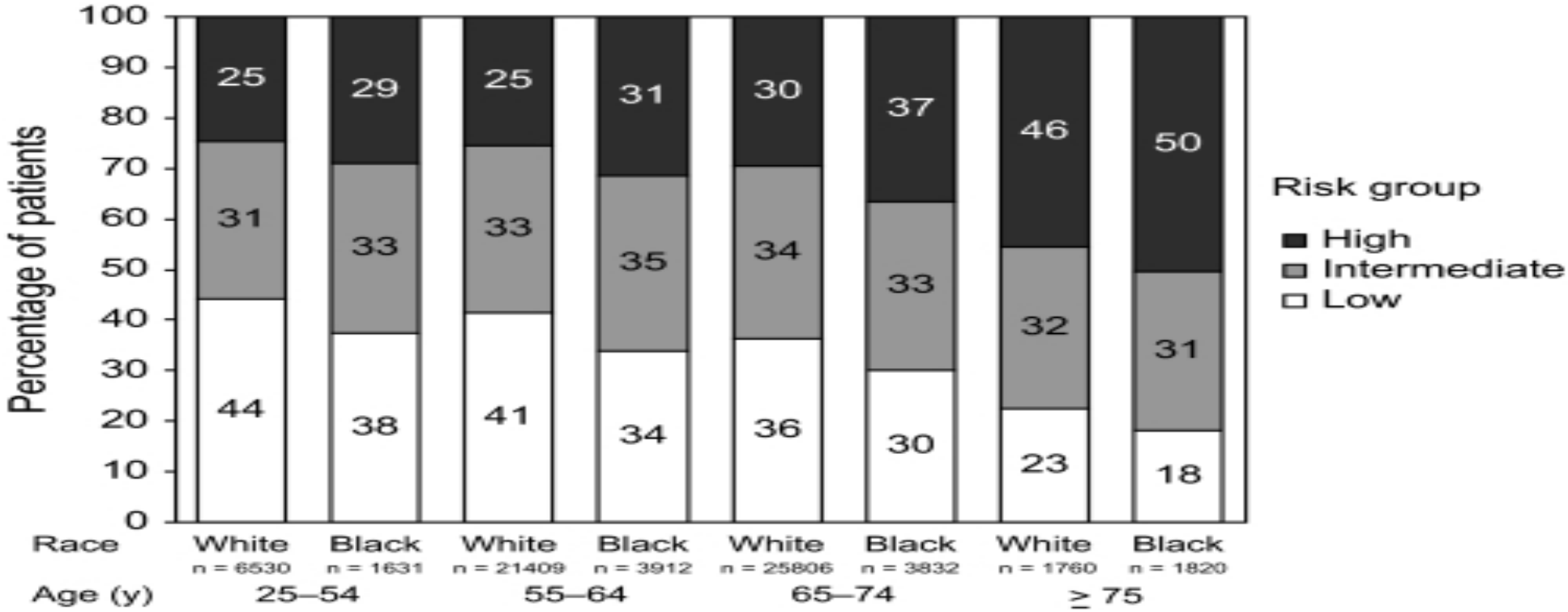
Changes in Risk Stratification in the PSA Era 1989-2002: CaPSURE



Cooperberg MR et al.; J Urol 2003 Dec:170(6Pt2):S21-25



20-35% of patients with newly diagnosed PCa are still classified as high risk, based on either PSA>20ng/ml, Gleason score >8 or an advanced clinical stage

Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst 2009 Sep 16;101(18):1280-3.
http://www.ncbi.nlm.nih.gov/pubmed/19713548

Patients classified with high-risk Pca are at an increased Risk of:

PSA failure
Need for secondary therapy
Metastatic Progression
Death from PCa

Yossepowitch O, Eggener SE, Bianco FJ Jr, et al. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol 2007 Aug;178(2):493-9; discussion 499.
http://www.ncbi.nlm.nih.gov/pubmed/17561152

Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update

Ian Thompson (Chair),* James Brantley Thrasher (Co-Chair),† Gunnar Aus,‡ Arthur L. Burnett,§ Edith D. Canby-Hagino, Michael S. Cookson,¶ Anthony V. D'Amico, Roger R. Dmochowski,‖ David T. Eton, Jeffrey D. Forman, S. Larry Goldenberg, Javier Hernandez, Celestia S. Higano, Stephen R. Kraus,** Judd W. Moul†† and Catherine M. Tangen (Prostate Cancer Clinical Guideline Update Panel)

Treatment of the High-Risk Patient

Option. Although active surveillance, interstitial prostate brachytherapy, EBRT, and RP are options for the management of patients with high-risk localized prostate cancer, recurrence rates are high.

Standard. High-risk patients who are considering specific treatment options should be informed of findings of recent high-quality clinical trials, including that:

- **When compared with WW, RP may lower the risk of cancer recurrence and improve survival;[10] and**
- **For those considering EBRT, use of hormonal therapy combined with conventional radiotherapy may prolong survival.[11,14]**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., for the SPCG-4 Investigators*

NEJM Mai 2011

the incidence in other studies[13,14]; nearly 80% of the men enrolled in our study had palpable tumors, with extracapsular tumor growth in 46% of the radical-prostatectomy specimens. All but five

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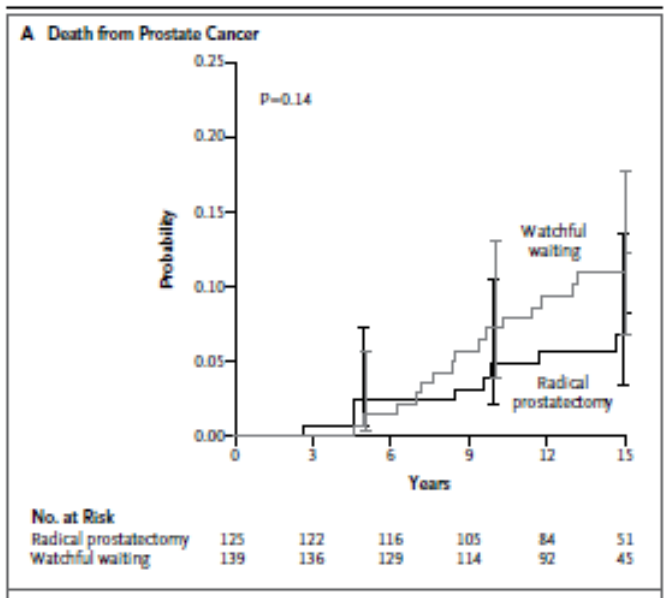
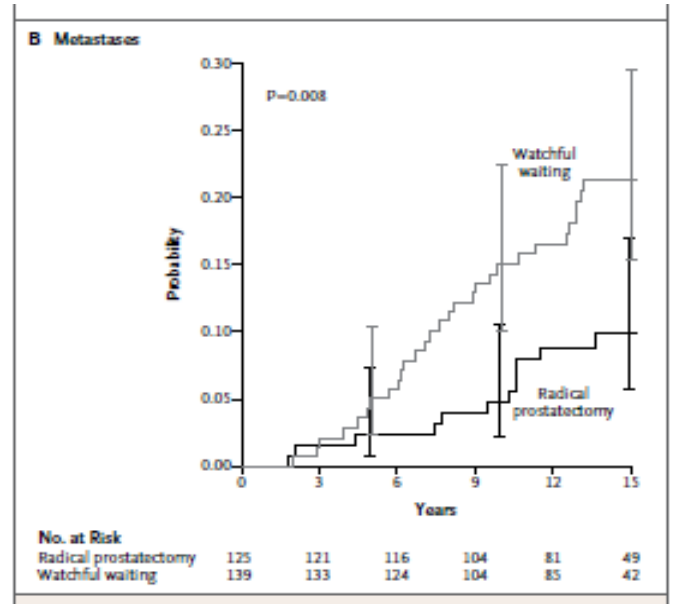




RESULTS

During a median of 12.8 years, 166 of the 347 men in the radical-prostatectomy group and 201 of the 348 in the watchful-waiting group died (P=0.007). In the case of 55 men assigned to surgery and 81 men assigned to watchful waiting, death was due to prostate cancer. This yielded a cumulative incidence of death from prostate cancer at 15 years of 14.6% and 20.7%, respectively (a difference of 6.1 percentage points; 95% confidence interval [CI], 0.2 to 12.0), and a relative risk with surgery of 0.62 (95% CI, 0.44 to 0.87; P=0.01). The survival benefit was similar before and after 9 years of follow-up, was observed also among men with low-risk prostate cancer, and was confined to men younger than 65 years of age. The number needed to treat to avert one death was 15 overall and 7 for men younger than 65 years of age. Among men who underwent radical prostatectomy, those with extracapsular tumor growth had a risk of death from prostate cancer that was 7 times that of men without extracapsular tumor growth (relative risk, 6.9; 95% CI, 2.6 to 18.4).

Gleason 8-10

Organ-confined disease is 26-31%.

One third with biopsy Gleason ≥8 show a Gleason of ≤7 in final histopathology.

Van Poppel H, Joniau S. An analysis of radical prostatectomy in advanced stage and high-grade prostate cancer. Eur Urol 2008 Feb;53(2):253-9.
http://www.ncbi.nlm.nih.gov/pubmed/17949893

25% positive lymph nodes

Schumacher MC, Burkhard FC, Thalmann GN, et al. Is pelvic lymph node dissection necessary in patients with a serum PSA <10ng/mL undergoing radical prostatectomy for prostate cancer? Eur Urol 2006 Aug;50(2):272-9.
http://www.ncbi.nlm.nih.gov/pubmed/16632187

N+ disease

Among patients with high-risk disease with N+ multiple series have demonstrated long-term cancer control after surgery with 10-yr CSS of up to 85%

Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol 2003;169:849–54.

Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004;172:2252–5.

Allaf ME, Palapattu GS, Trock BJ, Carter HB, Walsh PC. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. J Urol 2004;172:1840–4.

Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. J Urol 2007; 178:864–70.

Tumorregistry Munich

	Town of Munich	1,26 M
	Counties from 1978:	1,18 M
	Counties from 2002:	1,44 M
	Counties from 2007:	0,56 M
	total	**4,44 M**

End of 70ies

f / up in 96%

since 1988 all 6 Departments in Munich

European Association of Urology

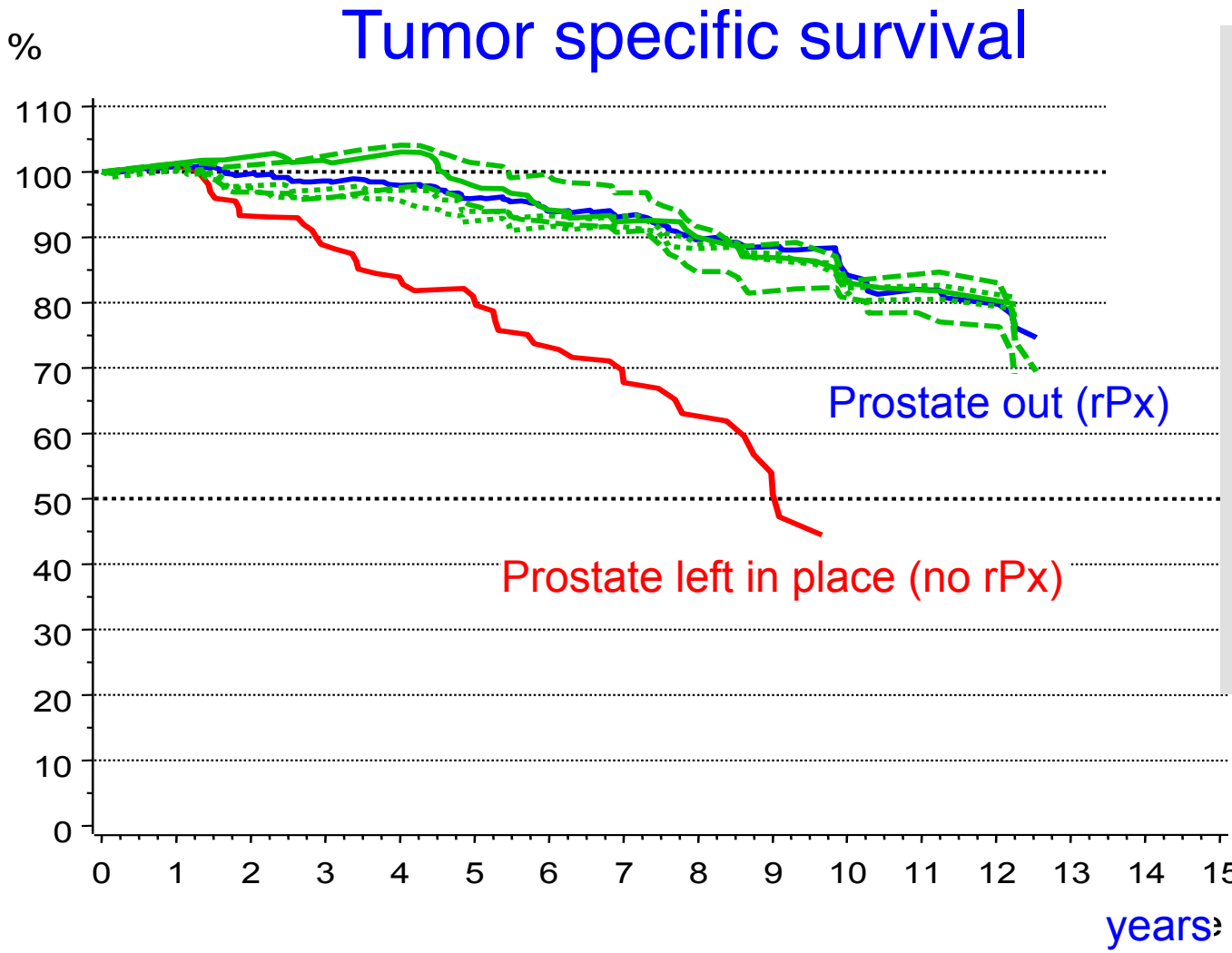
Tumorregistry Munich

Since 1988

35.629 PCA cases registered
27.956 primary PCA
13.805 with information on LN status
1.413 with positive LN
957 N+ and rPx
456 N+ without rPx

European Association of Urology

pN+: rPx vs prostate left in place



5 y survival

without rPx:	70%
with rPx:	95%
Difference 5y:	**25%**

10 y survival

without rPx:	40%
with rPx:	86%
Difference 10y:	**46%**

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pN+: rPx vs prostate left in place

Clear survival benefit for pN+ PCA when undergoing surgical removal of the prostate

EUROPEAN UROLOGY 57 (2010) 754–761

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

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Platinum Priority – Prostate Cancer

Editorial by Urs E. Studer, Laurence Collette and Richard Sylvester on pp. 762–763 of this issue

Survival Benefit of Radical Prostatectomy in Lymph Node–Positive Patients with Prostate Cancer

Jutta Engel[a,1,], Patrick J. Bastian[b,1], Helmut Baur[c], Volker Beer[d], Christian Chaussy[e], Juergen E. Gschwend[f], Ralph Oberneder[g], Karl H. Rothenberger[h], Christian G. Stief[b], Dieter Hölzel[a]*

European Association of Urology

pN+: adjuvant radiation

EUROPEAN UROLOGY 59 (2011) 832–840

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

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Combination of Adjuvant Hormonal and Radiation Therapy Significantly Prolongs Survival of Patients With pT2–4 pN+ Prostate Cancer: Results of a Matched Analysis

Alberto Briganti[a,*], *R. Jeffrey Karnes*[b], *Luigi Filippo Da Pozzo*[c], *Cesare Cozzarini*[d], *Umberto Capitanio*[a], *Andrea Gallina*[a], *Nazareno Suardi*[a], *Marco Bianchi*[a], *Manuela Tutolo*[a], *Andrea Salonia*[a], *Nadia Di Muzio*[d], *Patrizio Rigatti*[a], *Francesco Montorsi*[a], *Michael Blute*[b]

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[c] *Department of Urology, Ospedali Riuniti di Bergamo, Bergamo, Italy*
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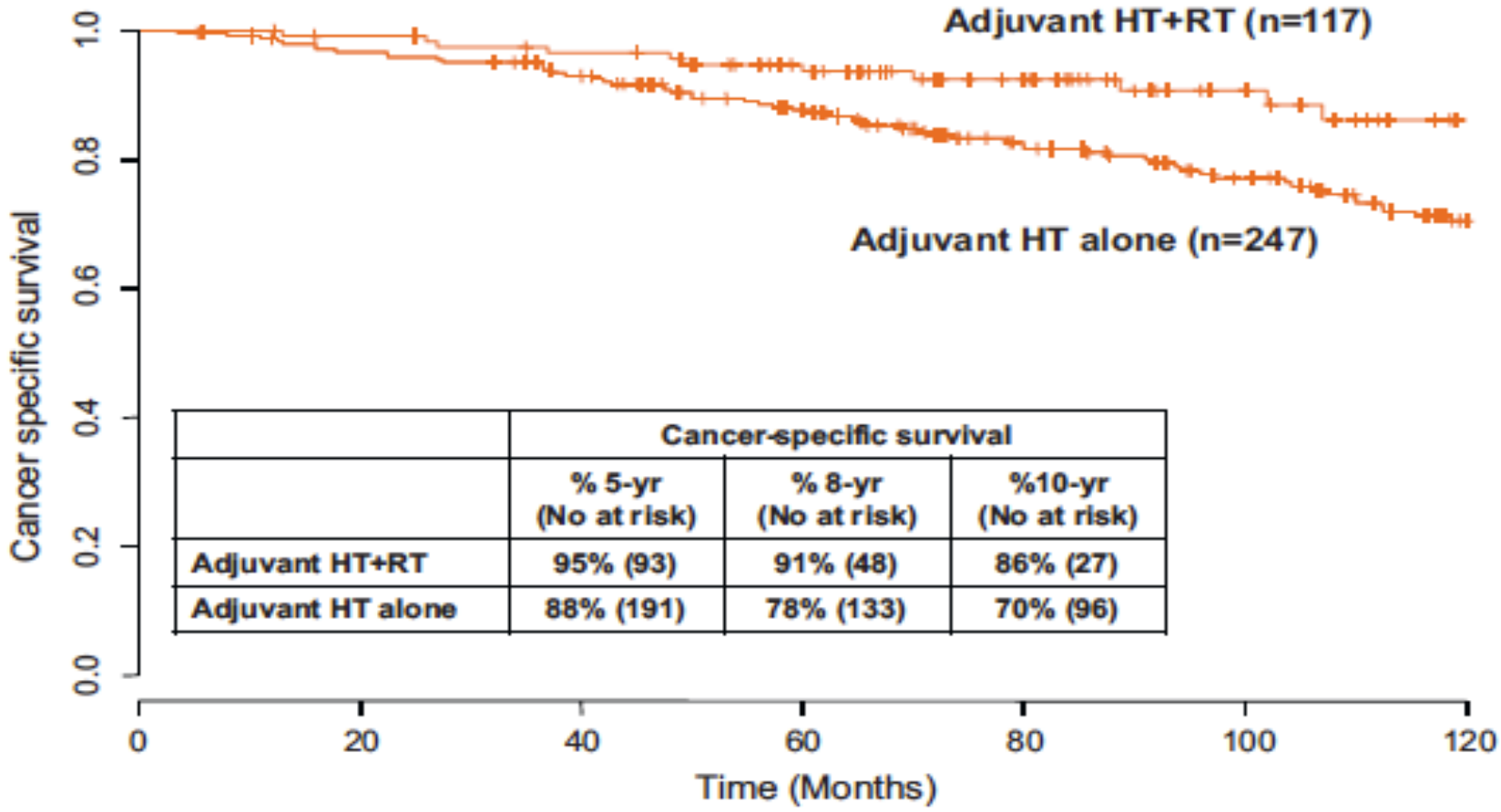
pN+: adjuvant radiation



	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	95% (93)	91% (48)	86% (27)
Adjuvant HT alone	88% (191)	78% (133)	70% (96)

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pN+: adjuvant radiation

further improvement of long-term survival in pN+ after rPx by adjuvant radiotherapy

PSA > 20ng/ml

PSA-failure rates between 44% (5a) and 53% (10a).

Yossepowitch O, Eggener SE, Bianco FJ Jr, et al. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol 2007 Aug;178(2):493-9; discussion 499.
http://www.ncbi.nlm.nih.gov/pubmed/17561152

PSA failure rate of 50% (5a).

D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999 Jan;17(1):168-72.
http://www.ncbi.nlm.nih.gov/pubmed/10458230

PSA > 20ng/ml

CSS of 90% (10a) and 85% (15a).n=712

Spahn M, Joniau S, Gontero P, et al. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. Eur Urol 2010 Jul;58(1):1-7; discussion 10-1.
http://www.ncbi.nlm.nih.gov/pubmed/20299147

CSS of 80%, 85% and 91% (10a)
in patients with PSA>100ng/ml; 50,1-100ng/ml; 20,1-50ng/ml

Gontero P, Spahn M, Tombal B, et al. Is there a prostate-specific antigen upper limit for radical prostatectomy? BJU Int 2011 Oct;108(7):1093-100.
http://www.ncbi.nlm.nih.gov/pubmed/21392220

cT3a PCa

Around 30% of diagnosed PCas today are locally advanced.

Several studies have demonstrated advantage of EBRT + ADT against EBRT without ADT.

So far no study demonstrating combined treatment being superior to RP

Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002 Jul;360(9327):103-6.
http://www.ncbi.nlm.nih.gov/pubmed/12126818

cT3a PCa

Positive margins are present in 33,5-66%.

Positive lymph nodes are found in 7,9-49%.

56-78% require adjuvant or salvage radiation.

but

Overstaging occurs in 13-27%.

Ward JF, Slezak JM, Blute ML, et al. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005 Apr;95(6):751-6.
http://www.ncbi.nlm.nih.gov/pubmed/15794776
Hsu CY, Joniau S, Oyen R, et al. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007 Jan;51(1):121-8; discussion 128-9.
http://www.ncbi.nlm.nih.gov/pubmed/16797831

EAU Guidelines 2012

cT3a PCa

Reference	no. of patients	Median and/ or mean follow-up	BPFS (%)			CSS (%)		
			5 years	10 years	15 years	5 years	10 years	15 years
Yamada *et al.* (1994) (49)	57	Median, 5.4 years	45.5 (PSA > 0.4)	-	-	-	-	-
Gerber *et al.* (1997) (50)	242	Mean, 39 months Median, 26 months	-	-	-	85	57	-
Van den Oudenet *al.* (1998) (51)	83	Median, 52 months	29 (PSA > 0.1)	-	-	85	72	-
Martinez de la Riva *et al.* (2004) (52)	83	Mean, 68.7 months (cT3a only)	- (PSA > 0.3)	59.8	-	100	-	-
Ward *et al.* (2005) (53)	841	Median, 10.3 years	58 (PSA > 0.4)	43	38	95	90	79
Hsu *et al.* (2007) (54)	200	Mean, 70.6 months (cT3a only)	59.5 (PSA > 0.2)	51.1	-	99	92	-

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High risk disease

.

Depending on definition of high risk disease CSS at 10 years varied beween 3-12%.

35-76% of patients remained free from additional therapy at 10years.

Loeb S, Schaeffer EM, Trock BJ, Epstein JI, Humphreys EB, Walsh PC. What are the outcomes of radical prostatectomy for high-risk prostate cancer? Urology 2010;76:710–4.

Yossepowitch O, Eggener SE, Serio AM, et al. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol 2008;53:950–9.

High risk disease

.

CSS of 95% (10a) after RP with only 24% adjuvant ADT and 8% adjuvant RT.(n=1513)

Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'Amico risk group classification for predicting survival following radical prostatectomy. J Urol 2008;179: 1354–61.

CCS of 81% (15a) after RP.

Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009;27: 4300–5.

Advantages of RP in High risk disease

Ability to obtain pathological staging, which may guide application of secondary therapies.

Patients with high-risk disease treated with radiation were 3.5 times more likely to receive ADT than after RP.

Meng MV, Elkin EP, Latini DM, et al. Treatment of patients with high risk localized prostate cancer: results from cancer of the prostate strategic urological research endeavor (CaPSURE). J Urol 2005;173:1557–61.

55-60% will have organ-confined disease.

Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'Amico risk group classification for predicting survival following radical prostatectomy. J Urol 2008;179: 1354–61.

Advantages of RP in High risk disease

Patients treated initially with RP and then salvage RT were less likely to wear pads and less likely to experience ED than patients treated with RT and then salvage RP .

Van Der Poel HG, Moonen L, Horenblas S. Sequential treatment for recurrent localized prostate cancer. J Surg Oncol 2008;97:377–82.

Advantages of RP in High risk disease

Several studies have shown in a retrospective non-randomized series improved survival for RP plus ADT against ADT alone.

Cadeddu JA, Partin AW, Epstein JI, Walsh PC. Stage D1 (T1–3,N1–3, M0) prostate cancer: a case-controlled comparison of conservative treatment versus radical prostatectomy. Urology 1997;50:251–5.

Ghavamian R, Bergstralh EJ, Blute ML, Slezak J, Zincke H. Radical retropubic prostatectomy plus orchiectomy versus orchiectomy alone for pTxN+ prostate cancer: a matched comparison. J Urol 1999;161:1223–7.

Grimm MO, Kamphausen S, Hugenschmidt H, Stephan-Odenthal M, Ackermann R, Vögeli TA. Clinical outcome of patients with lymph node positive prostate cancer after radical prostatectomy versus androgen deprivation. Eur Urol 2002;41:628–34.

Engel J, Bastian PJ, Baur H, et al. Survival benefit of radical prostatectomy in lymph node–positive patients with prostate cancer. Eur Urol 2010;57:754–61.

Steuber T, Budäus L, Walz J, et al. Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph

Functional Outcome after RP

.

Table 16: Complications of RP

Complication	Incidence (%)
Perioperative death	0.0-2.1
Major bleeding	1.0-11.5
Rectal injury	0.0-5.4
Deep venous thrombosis	0.0-8.3
Pulmonary embolism	0.8-7.7
Lymphocoele	1.0-3.0
Urine leak, fistula	0.3-15.4
Slight stress incontinence	4.0-50.0
Severe stress incontinence	0.0-15.4
Impotence	29.0-100.0
Bladder neck obstruction	0.5-14.6
Ureteral obstruction	0.0-0.7
Urethral stricture	2.0-9.0

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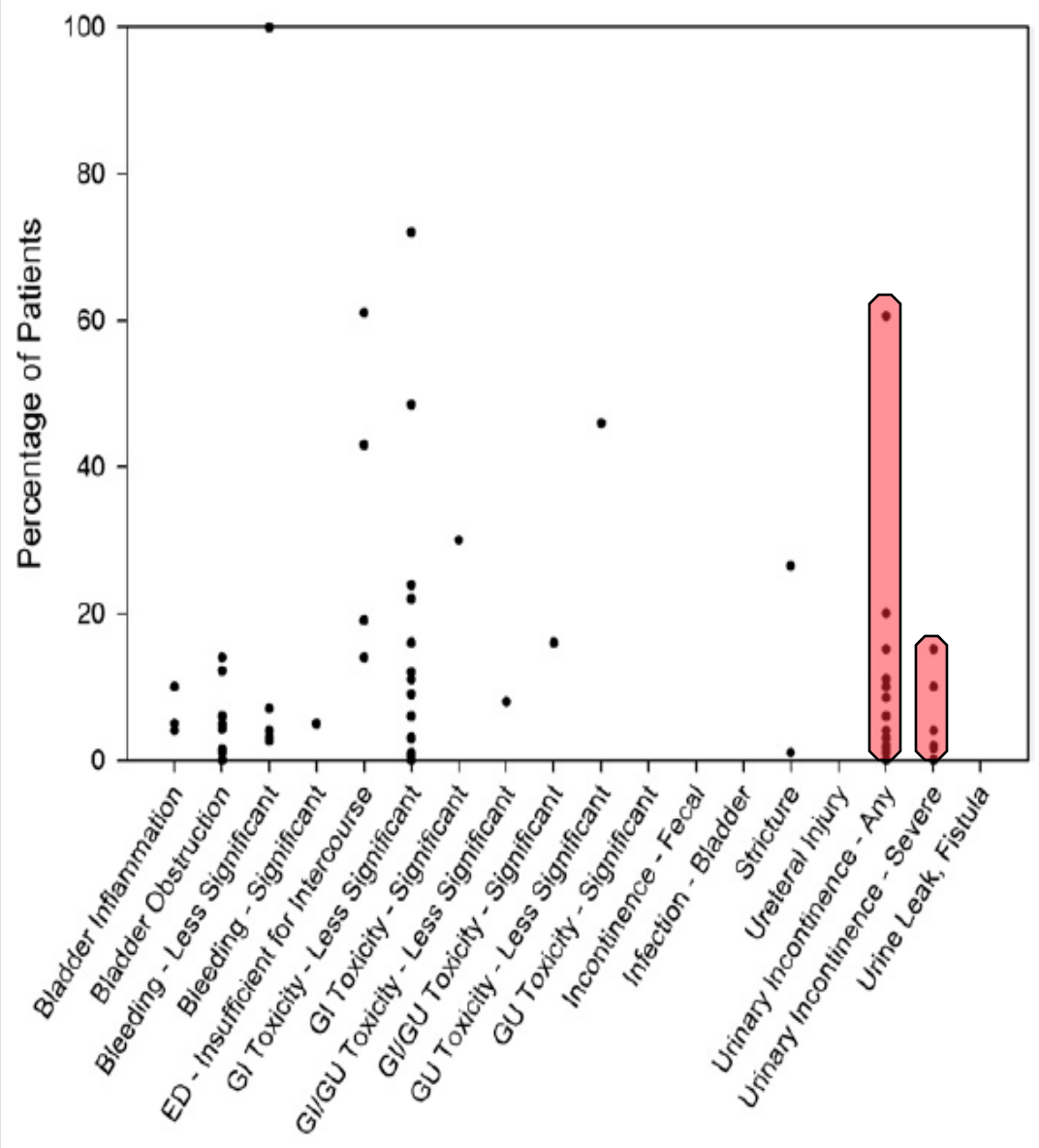


FIG. 3. Rate of complications reported with interstitial prostate brachytherapy.*

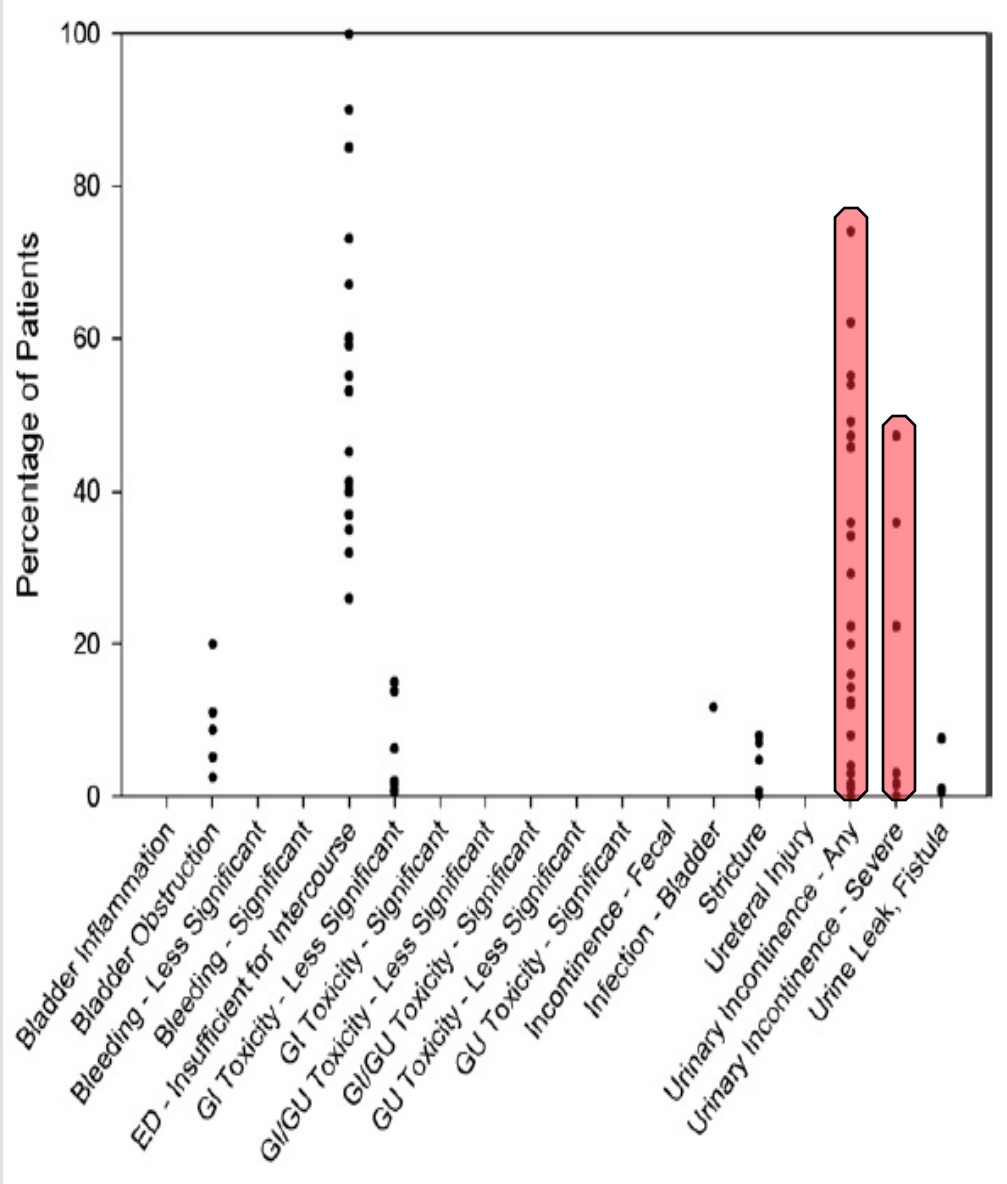
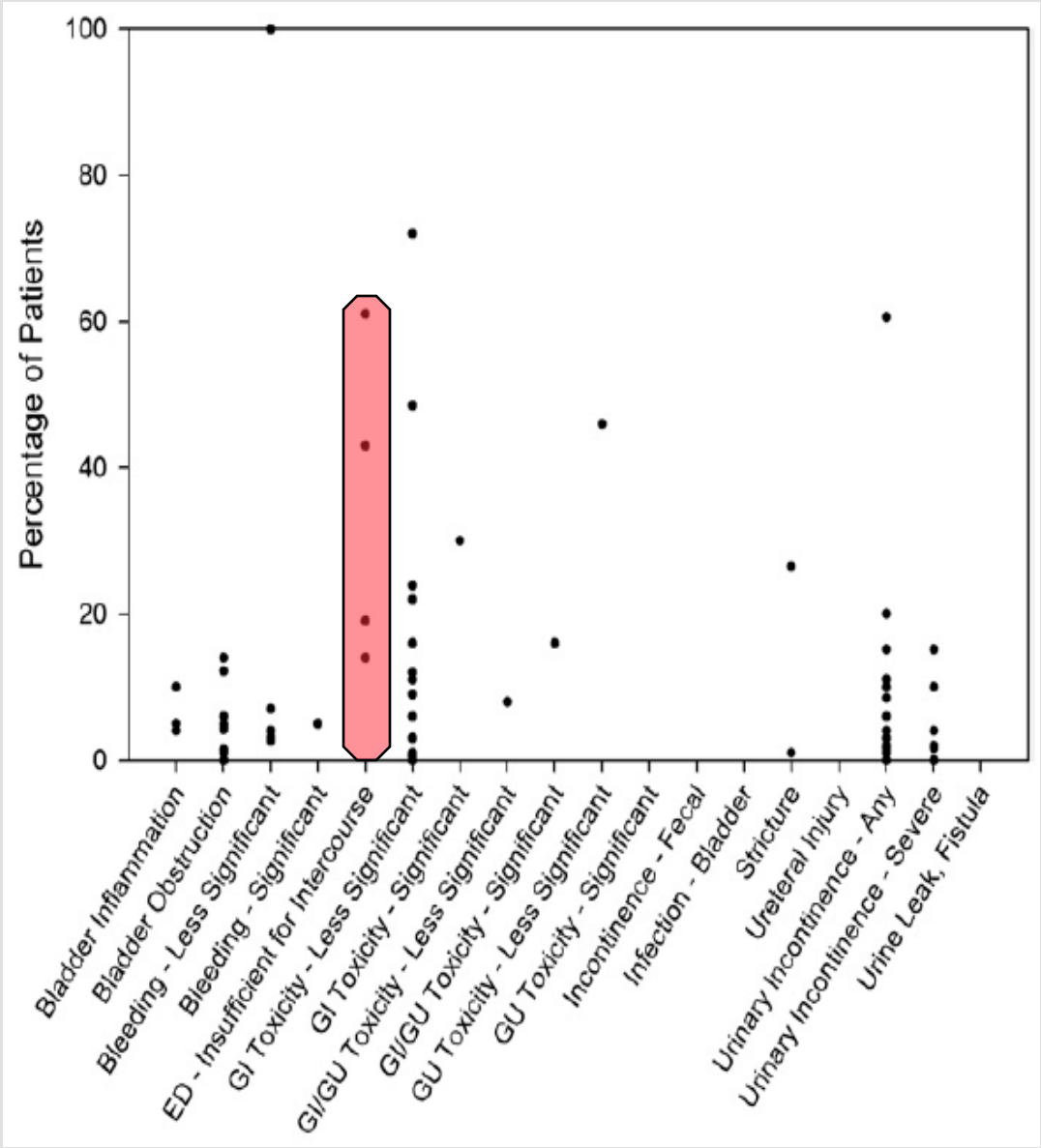


FIG. 5. Rate of complications reported with radical prostatectomy.*



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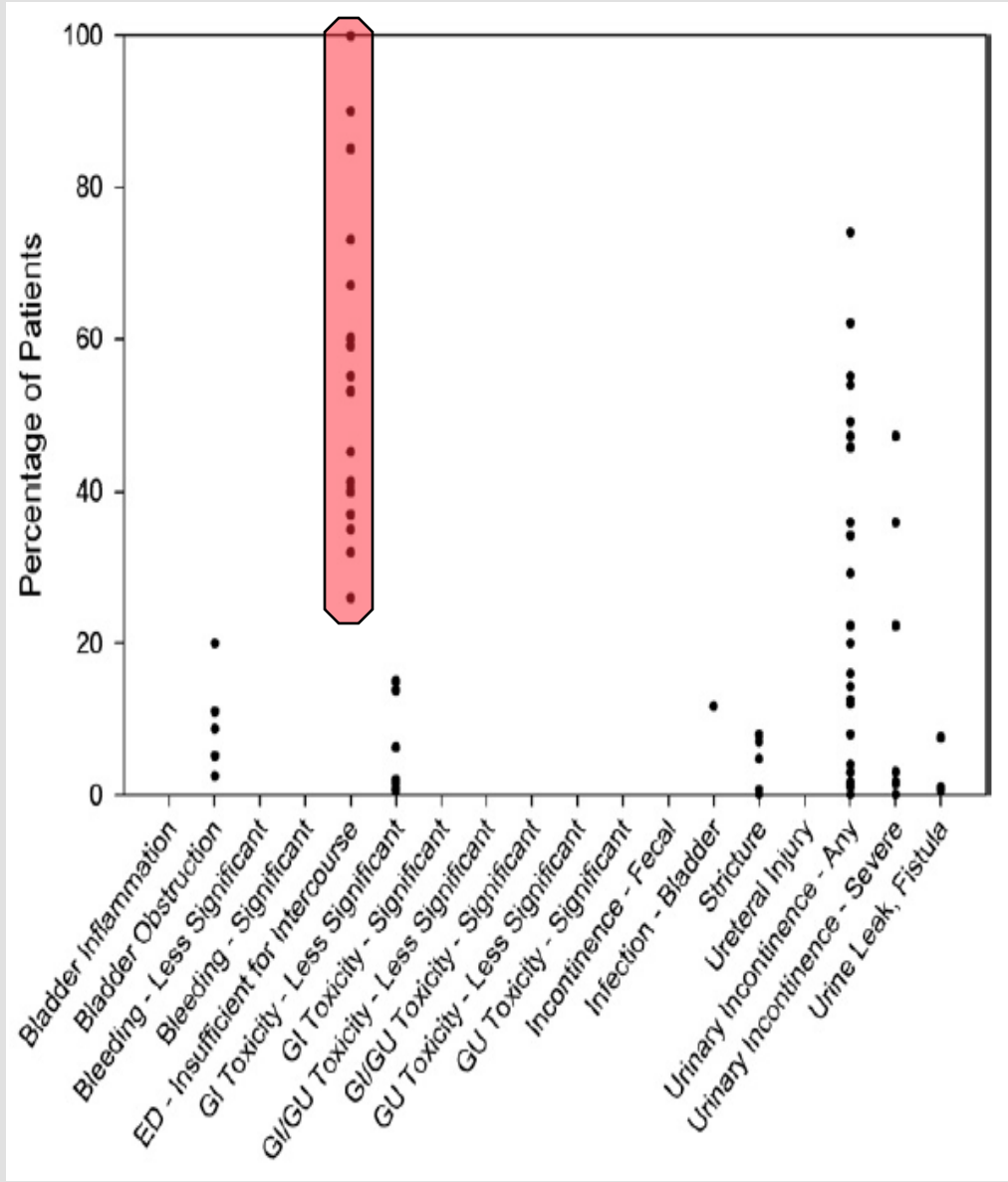

FIG. 5. Rate of complications reported with radical prostatectomy.*

Table 2 – Comparative series evaluating functional outcomes following surgery versus radiation for prostate cancer

Study	No. of patients			Assessment tool	Critical findings
	RP	EBRT	BT		
Litwin et al. [109]	307	78	90	SF-36, UCLA-PCI	1. Bowel dysfunction more common with either form of radiation than RP 2. Worse urinary control and sexual function with RP 3. No difference in urinary bother between treatments after 4 mo; no difference in sexual bother after 8 mo
Sanda et al. [3]	603	292	306	SCA, EPIC	1. All treatments affect sexual QoL 2. RP associated with urinary incontinence but improved scores on irritation and obstruction: moderate or worse urinary distress after 1 yr noted in 18% of BT, 11% EBRT, 7% RP 3. Reduced bowel function QoL after both forms of radiation but not RP
Pardo et al. [110]	123	127	185	SF-36, EPIC	1. 64% with baseline urinary irritative-obstructive symptoms improved after RP 2. BT and EBRT associated with worse urinary irritative-obstructive and bowel scores than RP 3. Greater deterioration in urinary continence and sexual function after RP

RP = radical prostatectomy; EBRT = external-beam radiation therapy; BT = brachytherapy; SF-36 = Short Form-36 Health Survery; UCLA-PCI = University of California-Los Angeles Prostate Cancer Index; SCA = Service Satisfaction Scale for Cancer Care; EPIC = Expanded Prostate Cancer Index Composite; QoL = quality of life.

Boorjian et al.; Eur Urol, 2012

Worse urinary control and sexual function with RP

Bowel dysfunction more common with radiation

Worse irritative and obstructive urinary function after radiation.

Summary

RP is a reasonable treatment option in selected patients with cT3a PCa, Gleason score 8-10 or PSA > 20. Furthermore, RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach.
Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.
If RP is performed, pelvic eLND must be performed, because lymph node involvement is common.
The patient must be informed about the likelihood of a multimodal approach. In case of adverse tumour characteristics (positive section margin, extraprostatic extension, or seminal vesicle invasion), adjuvant radiotherapy may reasonably be used after recuperation from surgery.
When nodal involvement is detected after surgery, adjuvant ADT may be selected.

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