A Brief Pitch for NTCP-Based Methodology

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Dose Limiting Toxicities/Endpoints?

- Hematologic in <33%
  - Grade 3 thombocytopenia w/ sig bleeding
  - Grade 3 neutropenia w/ fever/sequelae
  - Any grade 4 lasting >7d
- Kidney
  - Grade 3 CKD lasting >45d in <5%
  - Grade 3 AKI lasting <45d in <33%
- Salivary
  - Grade 3 in <5%
  - Grade 2 > 45d with PRO severe in <33%

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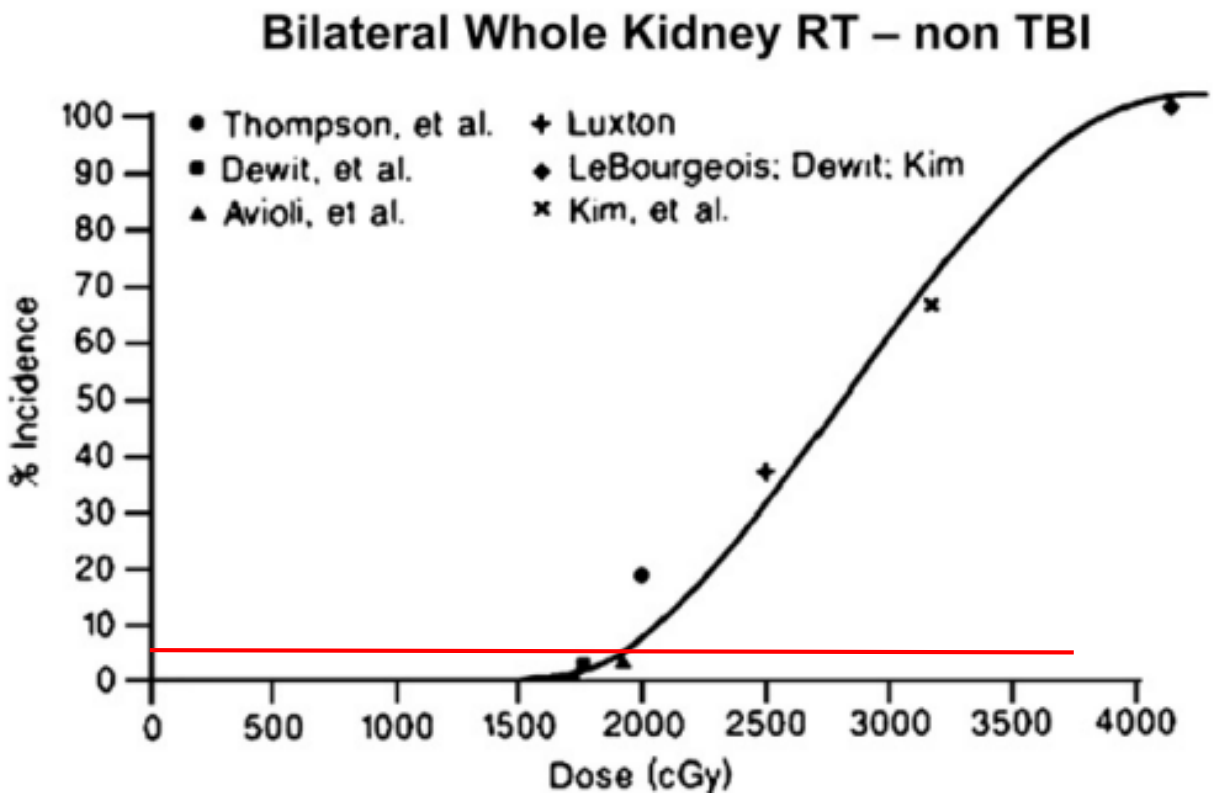
QUANTEC Nephropathy Normal Tissue Complication Probability (NTCP)



Mean dose <15–18 Gy to achieve <5% risk

Lyman-Burman-Kutcher normal tissue complication probability model parameters

Dawson QUANTEC 2010

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Meta-analysis of Lu-PSMA-RLT

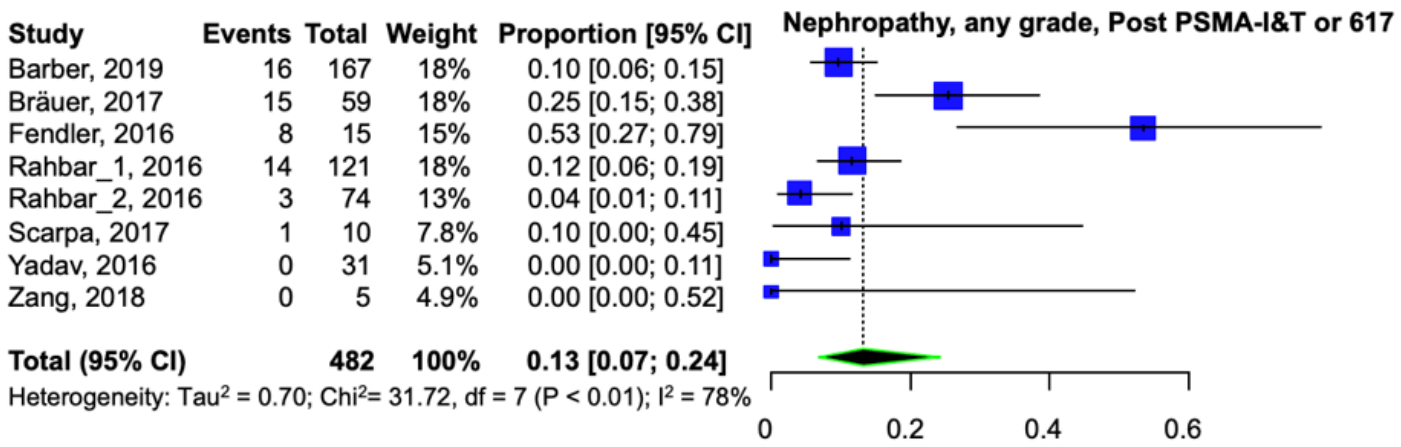

Fig 8-A, Nephropathy, any grade, Post PSMA-I&T or 617

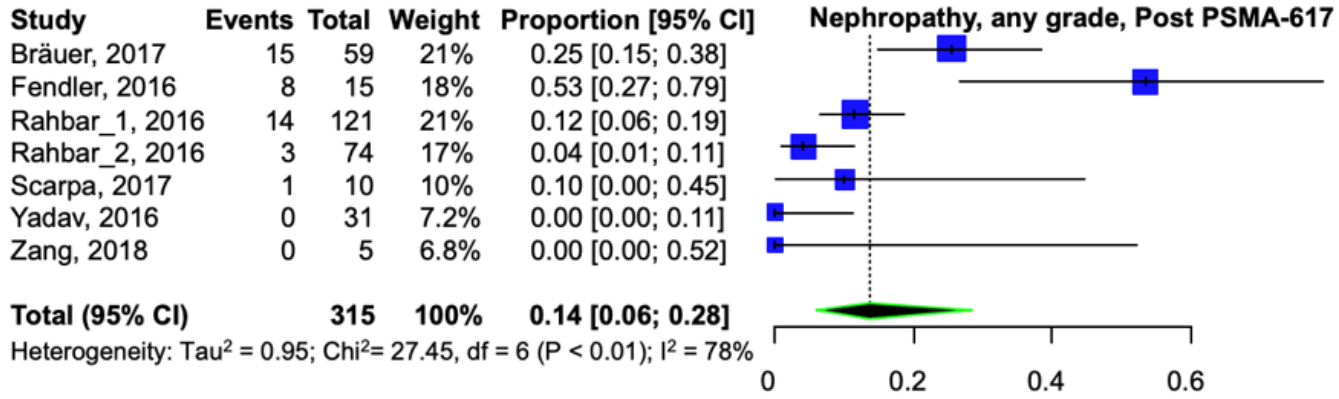

Fig 8-B, Nephropathy, any grade, Post PSMA-617

G1-2 Nephropathy reported

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Meta-analysis of Lu-PSMA-RLT

Study	Events	Total	Weight	Proportion [95% CI]
Barber, 2019	0	167	13%	0.00 [0.00; 0.02]
Bräuer, 2017	0	59	13%	0.00 [0.00; 0.06]
Fendler, 2016	0	15	12%	0.00 [0.00; 0.22]
Rahbar_1, 2016	0	121	13%	0.00 [0.00; 0.03]
Rahbar_2, 2016	0	74	13%	0.00 [0.00; 0.05]
Scarpa, 2017	0	10	12%	0.00 [0.00; 0.31]
Yadav, 2016	0	31	13%	0.00 [0.00; 0.11]
Zang, 2018	0	5	12%	0.00 [0.00; 0.52]
Total (95% CI)		**482**	**100%**	**0.01 [0.01; 0.04]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.00$, df = 7 (P = 0.7); $I^2 = 0\%$

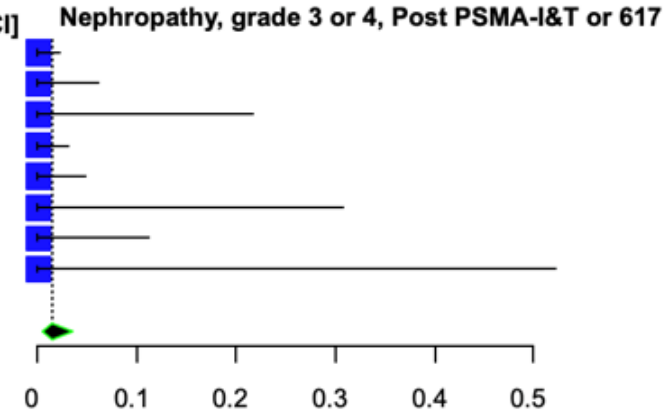

Fig 8-C, Nephropathy, grade 3 or 4, Post PSMA-I&T or 617

Study	Events	Total	Weight	Proportion [95% CI]
Bräuer, 2017	0	59	15%	0.00 [0.00; 0.06]
Fendler, 2016	0	15	14%	0.00 [0.00; 0.22]
Rahbar_1, 2016	0	121	15%	0.00 [0.00; 0.03]
Rahbar_2, 2016	0	74	15%	0.00 [0.00; 0.05]
Scarpa, 2017	0	10	14%	0.00 [0.00; 0.31]
Yadav, 2016	0	31	15%	0.00 [0.00; 0.11]
Zang, 2018	0	5	14%	0.00 [0.00; 0.52]
Total (95% CI)		**315**	**100%**	**0.02 [0.01; 0.05]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.67$, df = 6 (P = 0.7); $I^2 = 0\%$

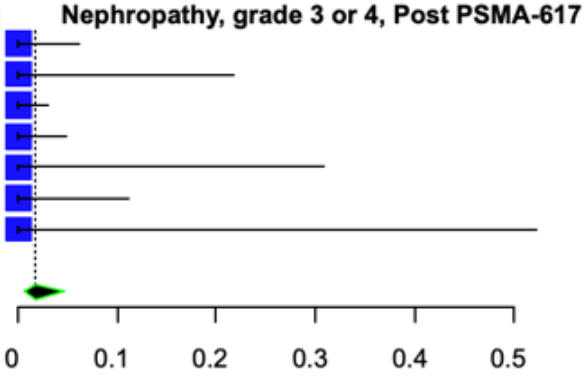

Fig 8-D, Nephropathy, grade 3 or 4, Post PSMA-617

G3-4 Nephropathy 0 in all
Weber TUM data is critical!

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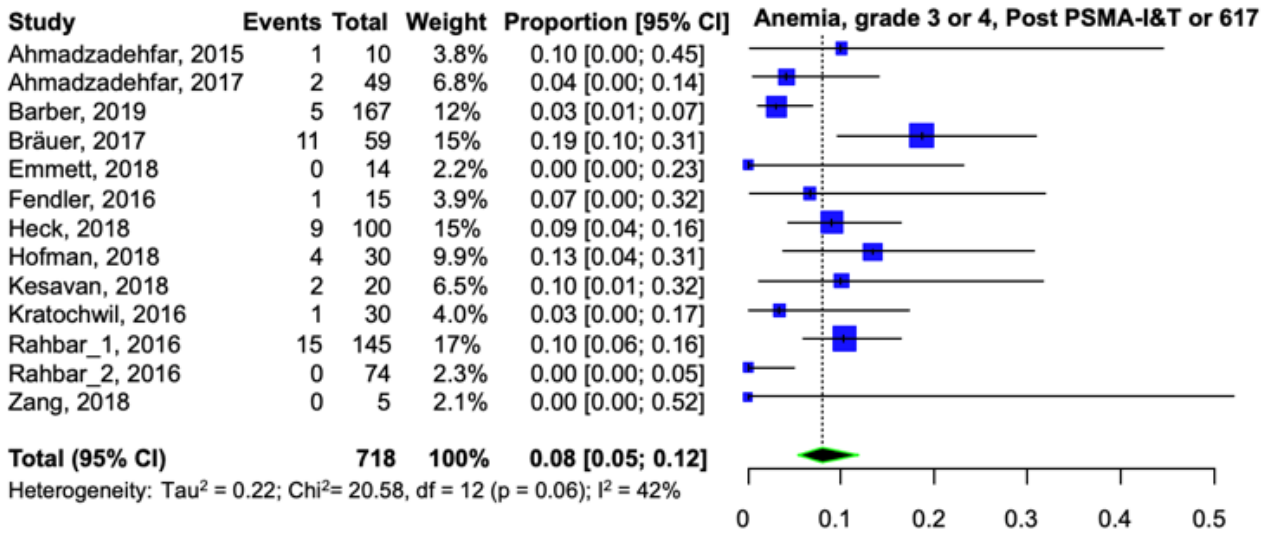

Fig 1-D, Anemia, grade 3 or 4, Post PSMA-I&T or 617

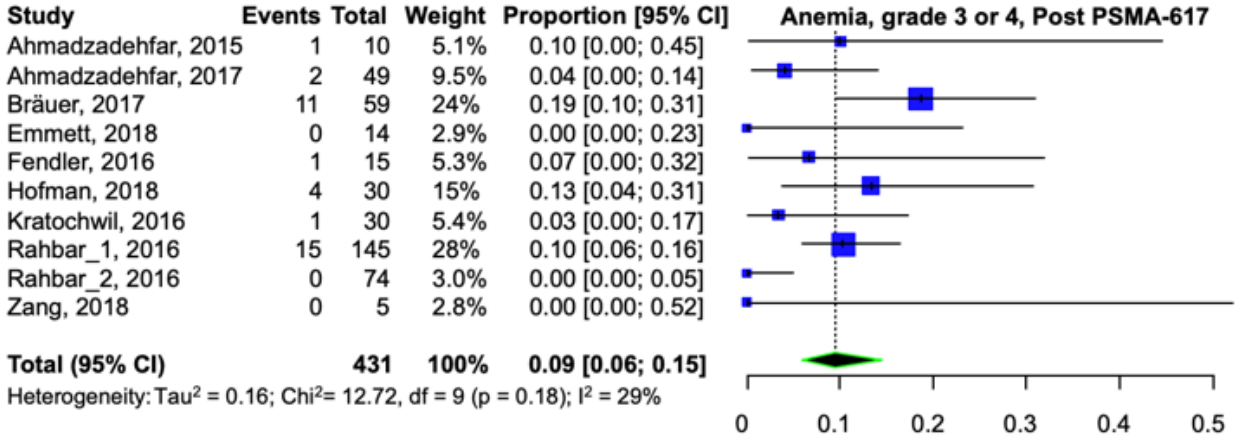

Fig 1-E, Anemia, grade 3 or 4, Post PSMA-617

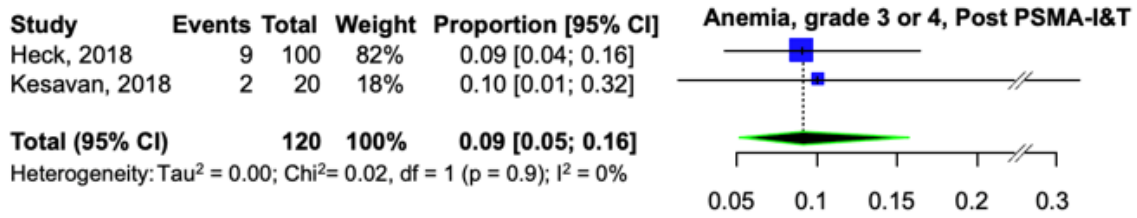

Fig 1-F, Anemia, grade 3 or 4, Post PSMA-I&T

G3-4 Anemia <33% in all
G3 vs G4 and outcome often unclear

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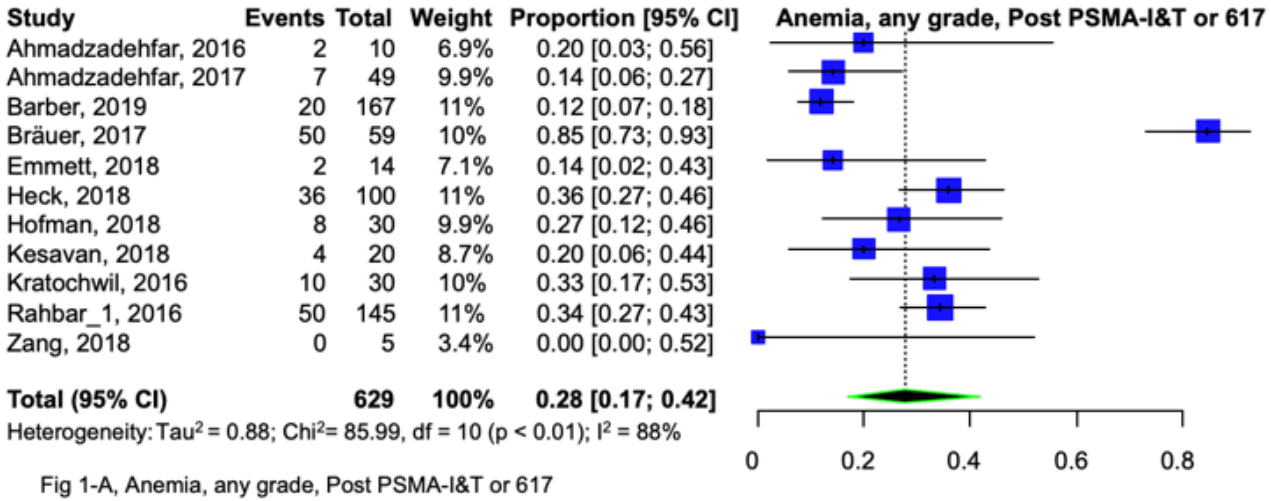

Fig 1-A, Anemia, any grade, Post PSMA-I&T or 617

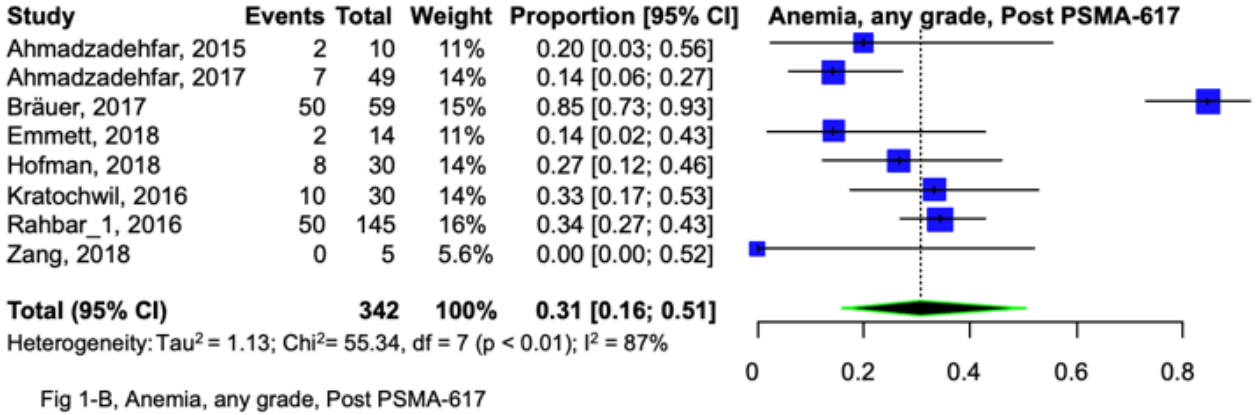

Fig 1-B, Anemia, any grade, Post PSMA-617

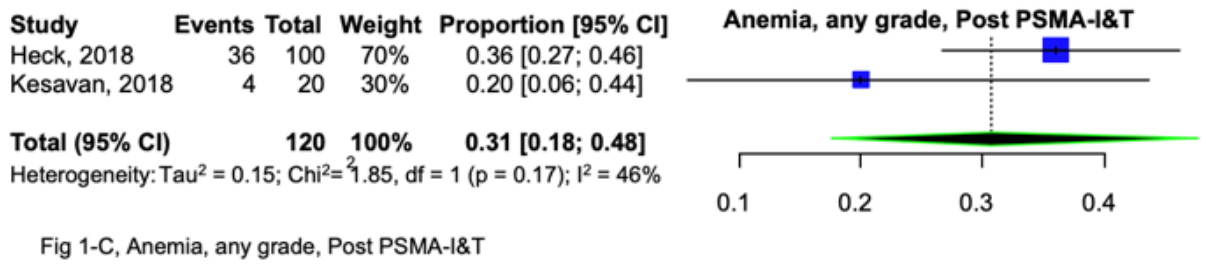

Fig 1-C, Anemia, any grade, Post PSMA-I&T

G1-2 Anemia more prevalent

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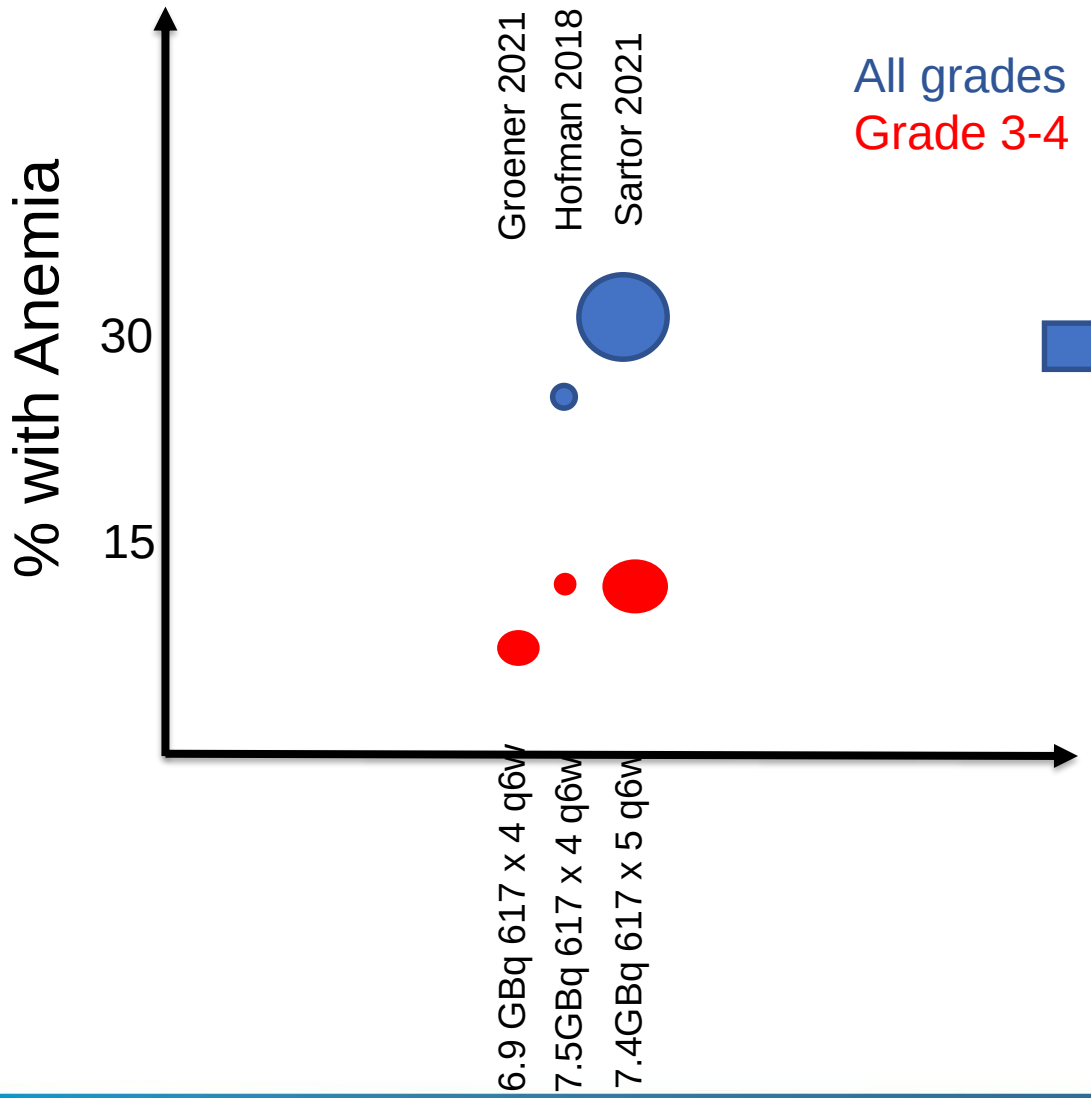
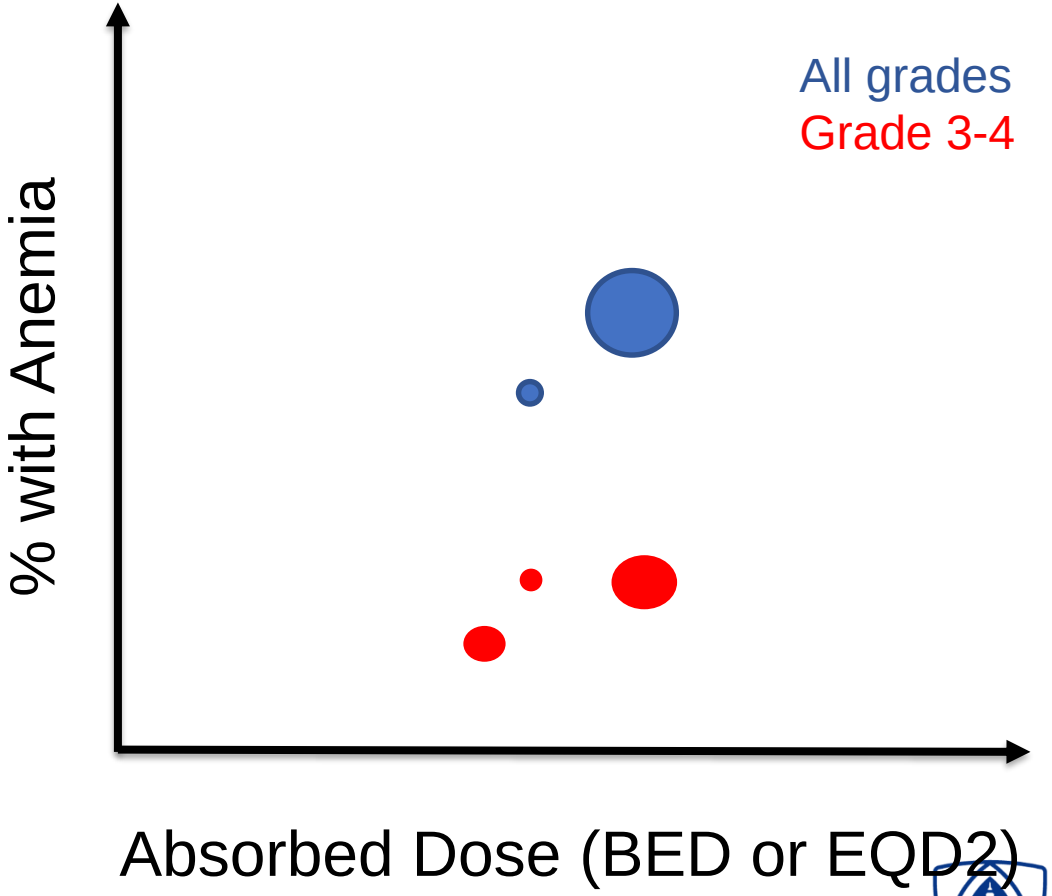
Lu-PSMA-RLT NTCP for Anemia





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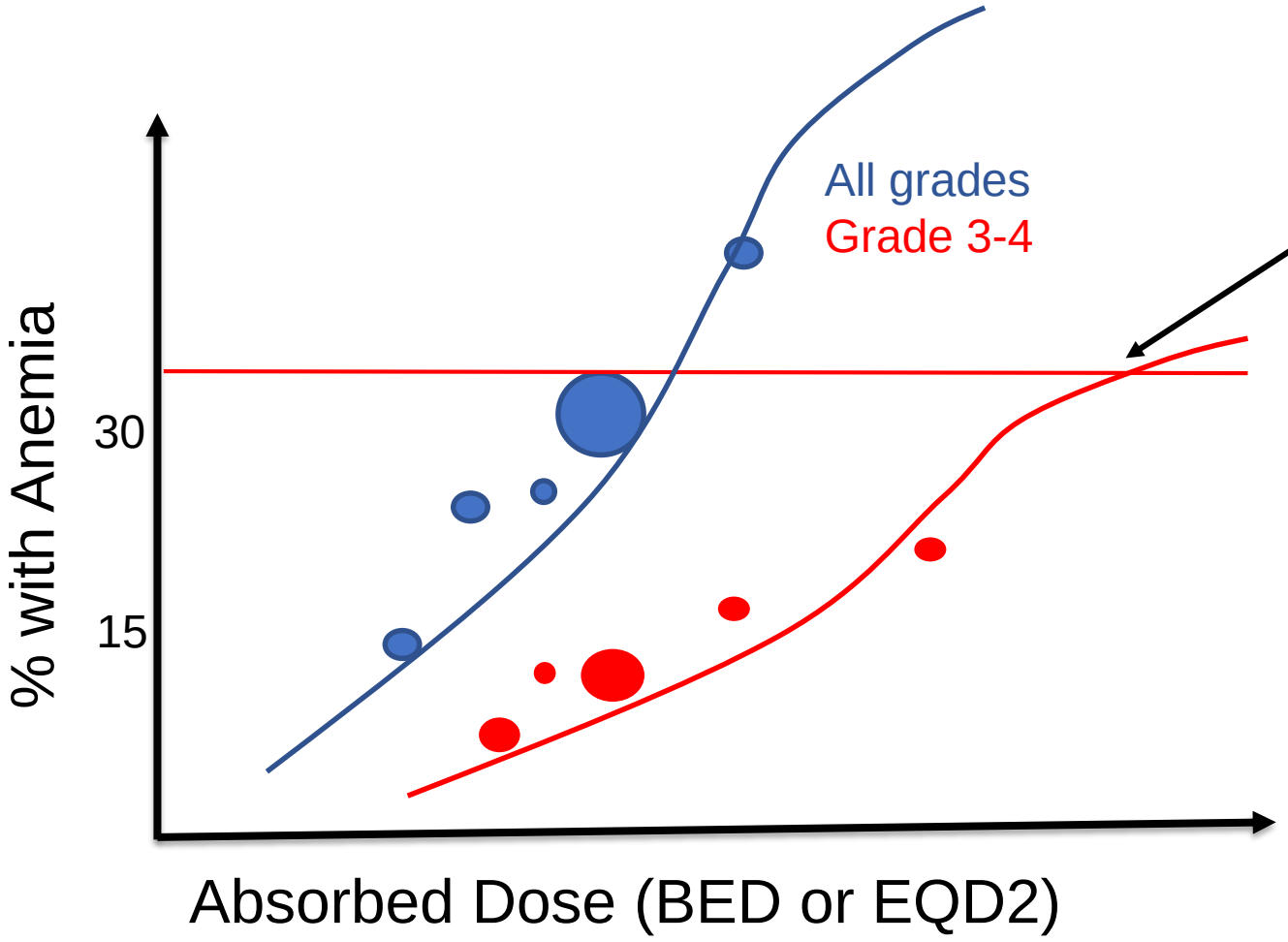
Lu-PSMA-RLT NTCP for Anemia



NOTA dose to achieve <33% risk g3 anemia

Probably need Soren Bentzen!

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Questions

Do you agree with using this method (where data applicable)?
Should we use median # cycles for each study (will slightly underestimate NOTA)?
Should we exclude studies with broad range of dose/cycle (if not able to separate tox)?
Should we train model with all grades or

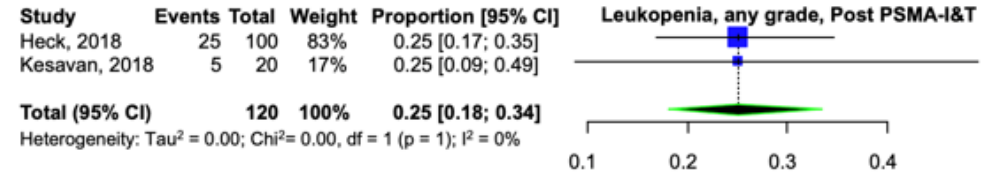

Fig 6-C, Leukopenia, grade 3 or 4, Post PSMA-I&T

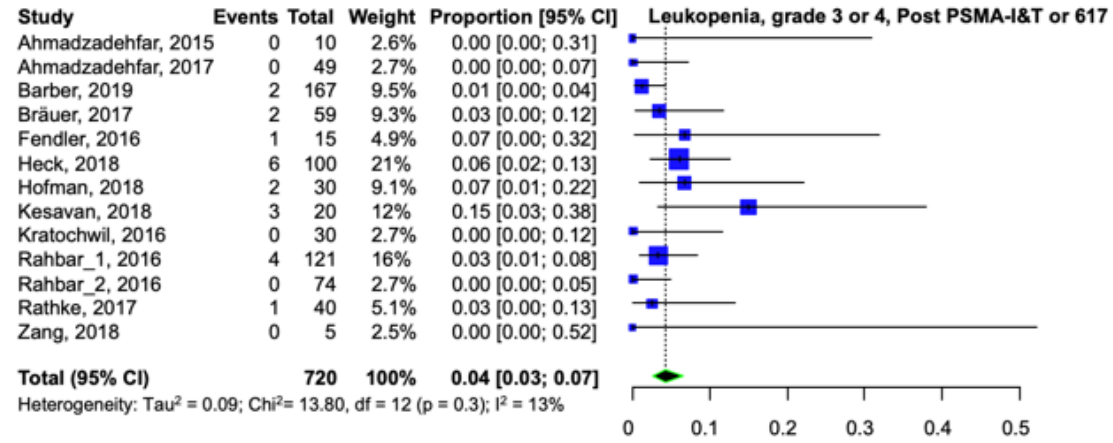

Fig 6-D, Leukopenia, grade 3 or 4, Post PSMA-I&T or 617

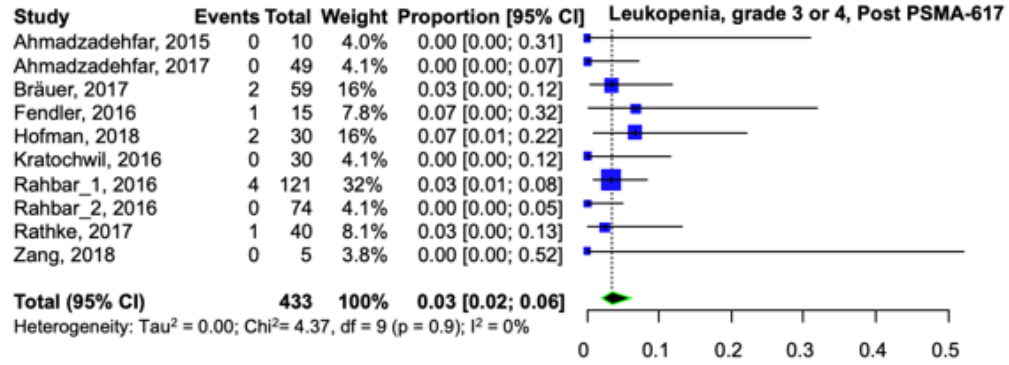

Fig 6-E, Leukopenia, grade 3 or 4, Post PSMA-617

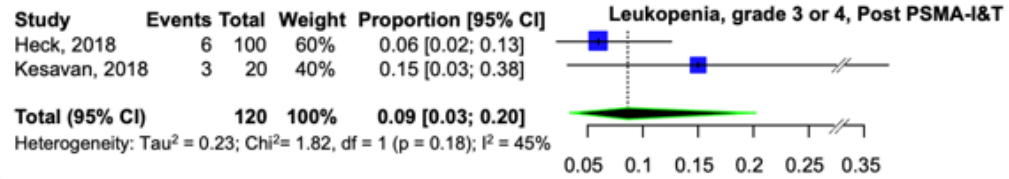

Fig 6-F, Leukopenia, grade 3 or 4, Post PSMA-I&T

G3-4 Leukopenia <33% in all studies
Uncertain if fever/sequelae
Uncertain if g4 resolved within 7d

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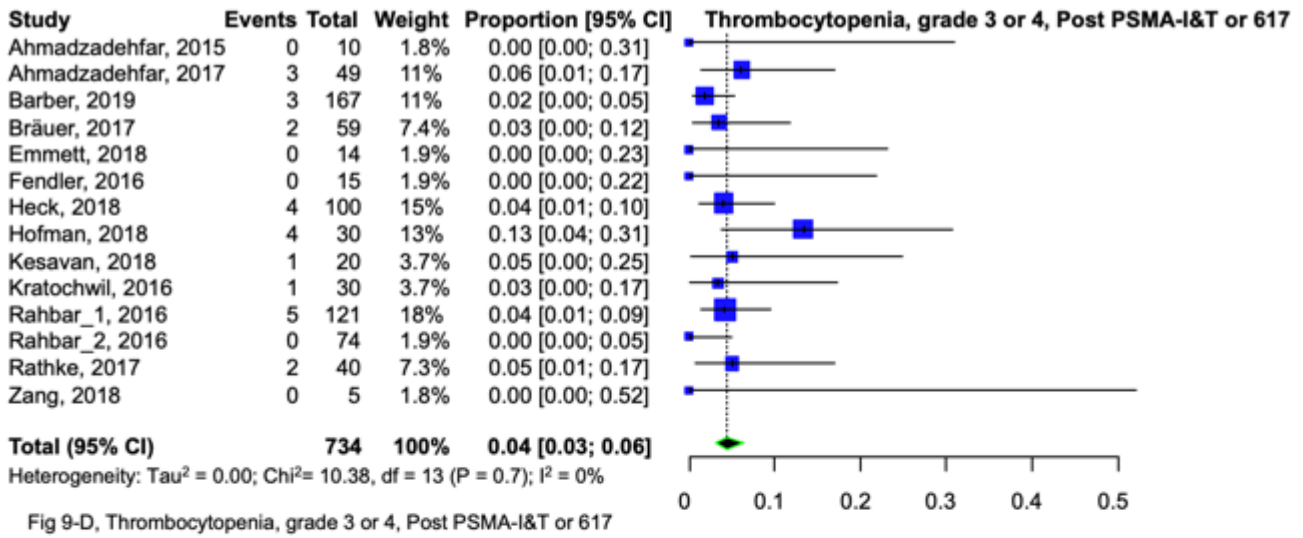

Fig 9-D, Thrombocytopenia, grade 3 or 4, Post PSMA-I&T or 617

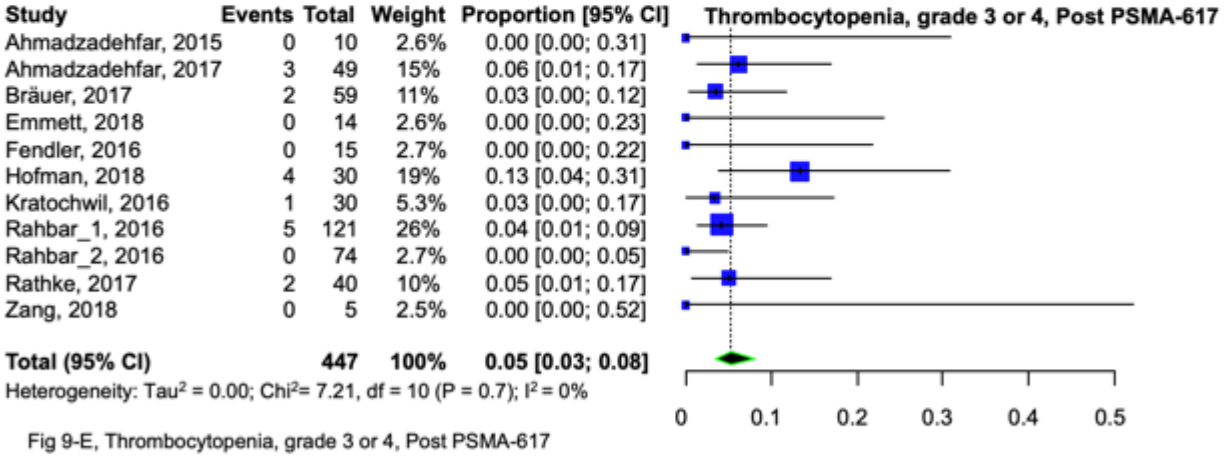

Fig 9-E, Thrombocytopenia, grade 3 or 4, Post PSMA-617

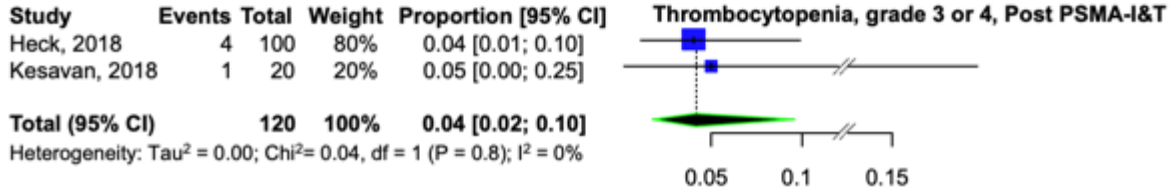

Fig 9-F, Thrombocytopenia, grade 3 or 4, Post PSMA-I&T

G3-4 Thrombocyopenia <33% in all
Uncertain if fever/sequelae
Uncertain if g4 resolved within 7d

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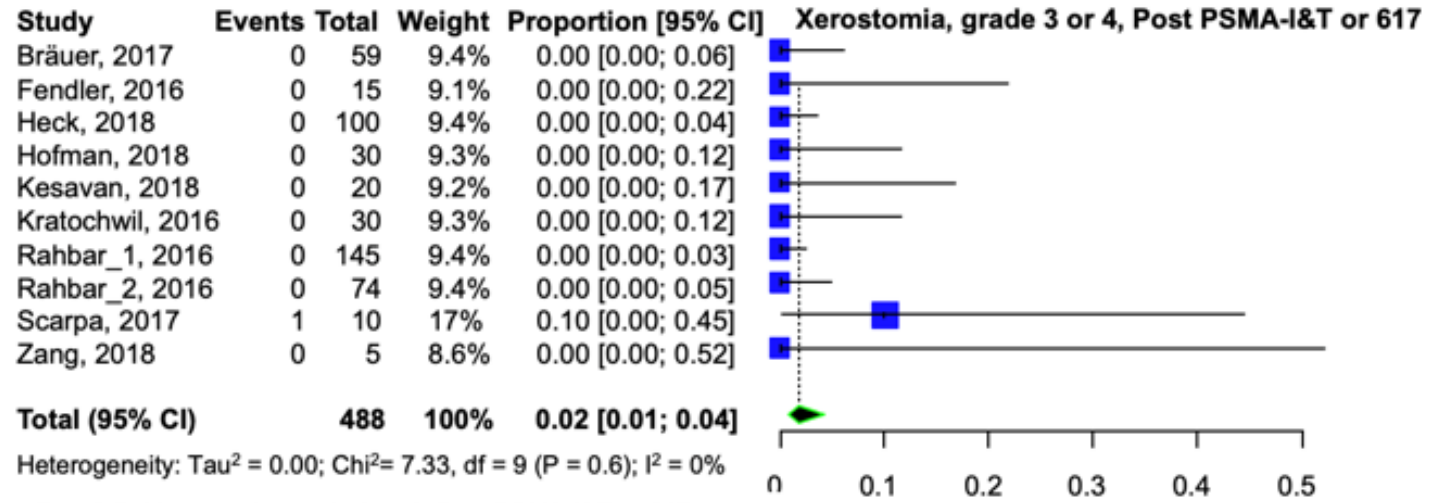


Fig 10-D, Xerostomia, grade 3 or 4, Post PSMA-I&T or 617

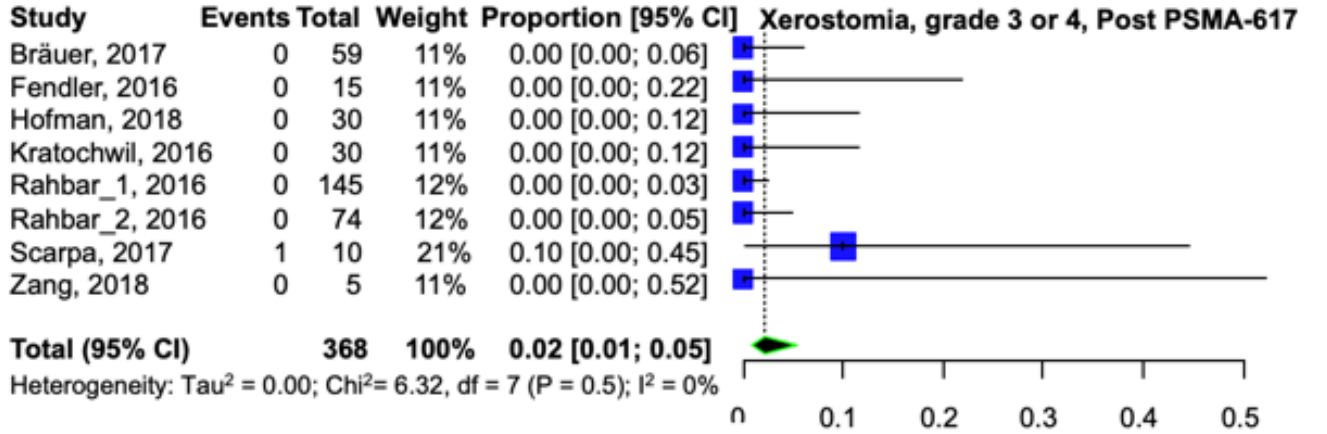
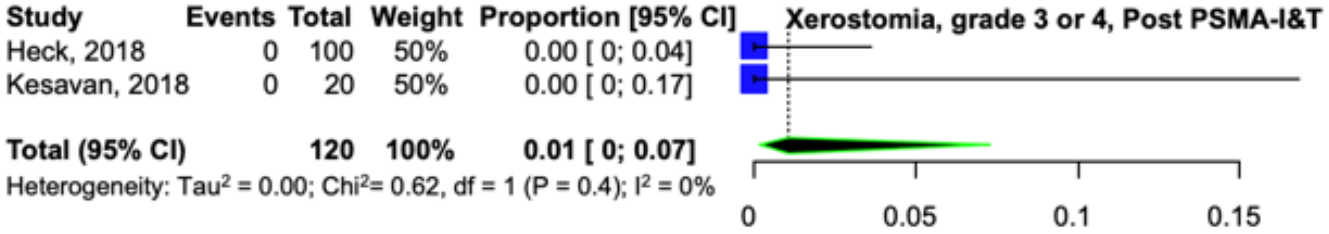


Fig 10-E, Xerostomia, grade 3 or 4, Post PSMA-617



G3-4 Xerostomia 10% in 1 study

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Grade 3 or 4 toxicity post ^{177}Lu-PSMA-617				
Toxicity	Estimated proportion	95% CI	I^2	p
Elevated ALT	0.03	[0.01;0.15]	41%	0.18
Anemia	0.09	[0.06; 0.15]	29%	0.18
Elevated AST	0.01	[0; 0.08]	17%	0.30
Diarrhea	0.01	[0; 0.06]	0	0.60
Fatigue	0.02	[0.01; 0.05]	0	0.64
Leukopenia	0.03	[0.02; 0.06]	0	0.89
Nausea	0.02	[0; 0.05]	0	0.43
Nephropathy	0.02	[0.01; 0.05]	0	0.72
Thrombocytopenia	0.05	[0.03; 0.08]	0	0.71
Xerostomia	0.02	[0.01; 0.05]	0	0.5
Grade 3 or 4 toxicity post ^{177}Lu-PSMA-I&T				
Toxicity	Estimated proportion	95% CI	I^2	p
Anemia	0.09	[0.05; 0.16]	0.0%	0.89
Leukopenia	0.09	[0.03; 0.20]	45%	0.18
Thrombocytopenia	0.04	[0.02; 0.10]	0	0.84
Xerostomia	0.01	[0; 0.07]	0	0.43

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^{177}Lu-PSMA-I&T/PNT2002

Toxicity	Grade	Administered Activity	Citations (N)	Comments
Xerostomia	1-2		Baum, Heck (100)	Acute, resolved
Leukopenia	1-2		Baum	Pts with prior long-term chemo
Nephrotoxicity		0.7-0.8 mGy/MBq	Baum, Okamoto, Acar (57)	Only 5% with worsening of prior CRI
Anemia, neutropenia, thrombocytopenia	3-4 in 9%, 6%, 4%		Heck (100)	

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^{225}Ac-PSMA-617

Kratochwil JNM 2017

Toxicity	CTCAE Grade	Administered activity	Citations	Comments
Xerostomia	1	100 kBq/kg x 1-4 cycles q8+ wks (4 of 4 pts)	Kratochwil	observed at 2–5 d, enduring for about 2 mo
	2	150 kBq/kg x 1-2 cycles (1 of 2 pts) 200 kBq/kg x 1 cycle (2 of 4 pts)	Kratochwil	discontinued therapy and used oral nutritional supplements; no feeding tubes (*g2 but likely unacceptable)
Nephrotoxicity	None	50-200 kBq/kg	Kratochwil	
Thrombocytopenia Leukopenia	2	200 kBq/kg (1 of 4 pts)	Kratochwil	

^{225}Ac-PSMA-617

Toxicity	CTCAE Grade	Administered Activity	Citations	Comments
Xerostomia	1 - 2 (17 of 17 pts)	8 MBq cycle 1, then de-esc to 4-7 MBq	Sathekge	None discontinued therapy
Nephrotoxicity	3 -> 4 (1 of 17 pts)	“	Sathekge	Solitary kidney and pre-treatment grade 3 renal failure
Anemia	2 -> 3 (1 of 17 pts)	“	Sathekge	Extensive bone marrow metastases and background anemia

Sathekge EJNMMI 2019

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^{225}Ac-PSMA-I&T

Toxicity	CTCAE Grade	Administered Activity	Citations	Comments
Xerostomia	1 - 2 (5 of 14)	7.8 MBq	Zacherl	
	8 with stable g1-2 from prior Lu-PSMA	"		
Nephrotoxicity	None	"		
Anemia	3 (3 of 14)	"		2 pts with prior g2
Leukopenia	3 (1 of 14)	"		

Zacherl JNM 2021

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^{225}Ac-PSMA-RLT

Toxicity	CTCAE Grade	Administered Activity	Citations	Comments
Xerostomia	1-2 (72%)	Various	Satapathy	PRISMA meta-analysis of 256 pts from 10 publications
	3 (1.2%)			
Nephrotoxicity	3 (3.8%)	“		
Anemia	3-4 (12.8%)	“		
Leukopenia	3-4 (8.3%)			
Thrombocytopenia	3-4 (6.3%)			

Satapathy Prostate CA Pros Dis 2021

Table 3 Toxicity profile of ^{225}Ac-PSMA radioligand therapy in the included studies.

Study	Total sample size	Adverse effects criteria	Salivary gland toxicity, n/N (%)		Hematotoxicity, n/N (%)		Nephrotoxicity, n/N (%)		Others, n/N (%)	Treatment stopped due to AE, n/N (%)	Treatment-related deaths, n/N (%)
			Any grade	Grade 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3			
Kratochwil et al. [14]	14	CTCAE v4.03	8/13 (62)	0/13 (0)	Anemia 2/14 (14); leucopenia 5/14 (36); thrombocytopenia 3/14 (21)	Anemia 1/14 (7); leucopenia 4/14 (28); thrombocytopenia 1/14 (7)	NS	NS	Grade 1/2 nausea, fatigue, and xerophthalmia in 1/14 (7)	1/14 (7); due to xerostomia and xerophthalmia	2/14 (14); combination with chemotherapy
Kratochwil et al. [15]	40	NS	NS	NS	NS	NS	NS	NS	NS	4/40 (10); due to xerostomia	NS
Sathekge et al. [16]	17	CTCAE v5.0	17/17 (100)	0/17 (0)	NS	NS	1/17 (6)	1/17 (6)	NS	0/17 (0)	NS
Sathekge et al. [17]	73	CTCAE v5.0	62/73 (85)	0/73 (0)	Anemia 27/73 (37); leucopenia 9/73 (12); thrombocytopenia 7/73 (10)	Anemia 5/73 (7); leucopenia 2/73 (3); thrombocytopenia 1/73 (1)	23/73 (32)	5/73 (7)	Grade 1/2 nausea 15/73 (21), anorexia 23/73 (32), constipation 19/73 (26), fatigue 37/73 (51), weight loss 28/73 (38), hypoalbuminemia 14/73 (19), dysuria 13/73 (18), xerophthalmia 4/73 (6)	0/73 (0)	NS
Khreish et al. [18]	20	CTCAE v4.0	13/20 (65)	0/20 (0)	NS	Anemia 3/20 (15); leucopenia 2/20 (10); thrombocytopenia 2/20 (10)	NS	0/20 (0)	Grade 1 nausea 1/20 (5), fatigue 5/20 (25), anorexia 4/20 (20)	NA	0/20 (0)
Yadav et al. [19]	28	CTCAE v5.0	8/28 (29)	0/28 (0)	Anemia 28/28 (100); leucopenia 11/28 (39); thrombocytopenia 4/28 (14)	Anemia 1/28 (4); leucopenia 0/28 (0); thrombocytopenia 0/28 (0)	4/28 (14)	0/28 (0)	Grade 1/2 fatigue 14/28 (50), Grade 3 fatigue 1/28 (4)	NS	NS
Zacherl et al. [20]	14	CTCAE v5.0	5/14 (36)	0/14 (0)	Anemia 14/14 (100); leucopenia 5/14 (36); thrombocytopenia 6/14 (43)	Anemia 3/14 (21); leucopenia 1/14 (7); thrombocytopenia 0/14 (0)	2/14 (14)	0/14 (0)	Grade 1/2 nausea 5/14 (36), anorexia 9/14 (64), fatigue 12/14 (86), weight loss 4/14 (29), dysgeusia 6/14 (43)	4/14 (28); due to xerostomia in 3 patients and grade 3 leucopenia in 1 patient	NS
Satapathy et al. [21]	11	CTCAE v5.0	8/11 (73)	1/11 (9)	Anemia 8/11 (73); leucopenia 5/11 (46); thrombocytopenia 5/11 (45)	Anemia 1/11 (9); leucopenia 0/11 (0); thrombocytopenia 2/11 (18)	1/11 (9)	1/11 (9)	Grade 1/2 nausea 2/11 (18), constipation 2/11 (18), fatigue 3/11 (27), weight loss 2/11 (18), anorexia 3/11 (27)	3/11 (27); due to grade 3 thrombocytopenia in 2 patients and grade 3 nephrotoxicity in 1 patient	3/11 (27)
Feuerecker et al. [22]	26	CTCAE v5.0	26/26 (100)	0/26 (0)	Anemia 15/26 (58); leucopenia 13/26 (50); thrombocytopenia 14/26 (54)	Anemia 9/26 (35); leucopenia 7/26 (27); thrombocytopenia 5/26 (19)	5/26 (19)	0/26 (0)	Grade 1 fatigue 12/26 (36), loss of weight 3/26 (12), anorexia 8/26 (31)	8/26 (31); due to xerostomia in 6 patients and to avoid worsening of pre-existing leucopenia and thrombocytopenia in 1 patient each	NS
van der Doelen et al. [23]	13	CTCAE v5.0	13/13 (100)	0/13 (0)	NS	Anemia 0/13 (0); leucopenia 0/13 (0); thrombocytopenia 0/13 (0)	NS	0/13 (0)	NS	0/13 (0)	NS

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^{177}Lu-PSMA-617 and I&T meta-analysis

Toxicity	Grade	Administered Activity	Citations (N)	Comments
Xerostomia	g3-4 in 2%	Various	Rowe 2021 (488 pts in 10 studies)	
Leukopenia	g3-4 in 4%		Rowe 2021 (720 pts in 13 studies)	
Anemia	g3-4 in 8%		Rowe 2021 (718 pts in 13 studies)	
Thrombocytopenia	g3-4 in 4%		Rowe 2021 (734 pts in 14 studies)	
Nephrotoxicity	g3-4 in 1%		Rowe 2021 (482 pts in 8 studies)	

Rowe EU 2021

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