TCP in anal cancer

Anders Johnsson
Dept of Oncology
Lund

Radiotherapy dosing

- Guidelines recommend 50-60 Gy with FUMI
- Rather effective (70-80% cured) – but toxic (late sequele)
- Optimal RT dose for the individual patient unknown

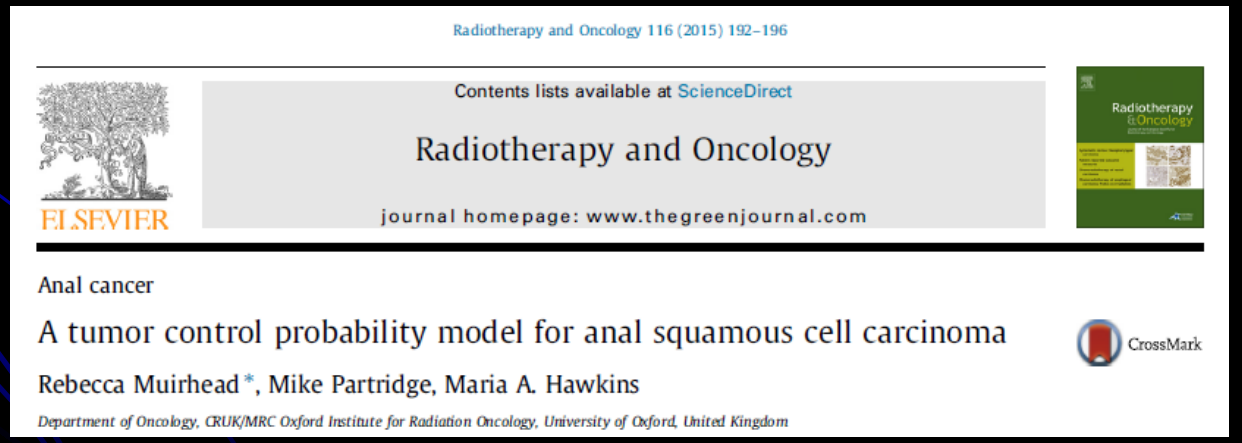
- *We need to know more*
- *Relations between RT dose and effect?*
- *Other factors of importance? Tumor size?*

TCP studies in anal cancer

- Muirhead et al 2015
- Our own study on the NOAC database 2018

TCP anal cancer

- Based on 13 studies (n=645 patients)
- Impact of tumor size on TCP?
- Not individual patient data



Radiotherapy and Oncology 116 (2015) 192–196

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Anal cancer

A tumor control probability model for anal squamous cell carcinoma

Rebecca Muirhead *, Mike Partridge, Maria A. Hawkins

Department of Oncology, CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, United Kingdom

TCP modelling

IMRT publications identified for use within the standard linear-quadratic model to create the TCP model.

		No. of patients	T1/T2 (%)	T3/4 (%)	Median dose delivered (Gy)	Median overall treatment time (days)	2 year local control unless stated (%)	FU median (months)
Milano et. al. [27]	2005	17	47.1	52.3	52.3	39*	82	20
Salama et al. [26]	2007	53	60.4	37.8	51.5	42	83.9 (18 months)	14.5
Pepek et al. [27]	2010	31	N/R	N/R	54.0	40*	100	19
Bazan et al. [28]	2011	29	72.4	27.6	54.0	40	92 (3 years)	32
Vieillot et al. [29]	2012	39	36.0	64.0	63.0	50	77	24
De Foe et al. [30]	2012	78	65.4	30.8	55.8	50	83.2	19.8
Dewas et al. [31]	2012	24	47.8	52.2	59.4	47	63	40
Kachnic et al. [32]	2012	43	67.0	14.0	52.2	39*	95	24
Deenen et al. [33]	2012	18	33.3	66.7	63.0	47*	89	28
Chuong et al. [34]	2013	52	55.8	44.2	56.0	38.5	90.8	19
Dasgupta et al. [35]	2013	45	64.3	31.2	54.0	40	87	27.5
Call et al. [36]	2014	148	72.0	28.0	51.3	40	87 (3 yrs)	26.8
Koerber et al. [37]	2014	68	69.1	30.9	54.5	37*	83	30.8

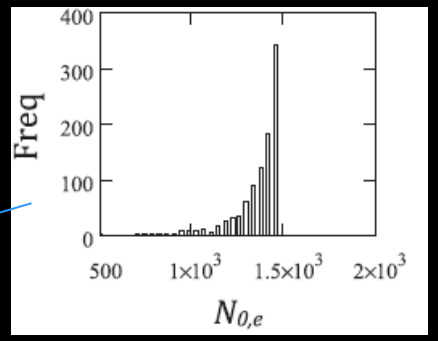
* Median overall treatment time not reported for the IMRT group therefore an estimation was calculated using dose/dose per fraction and interruptions.

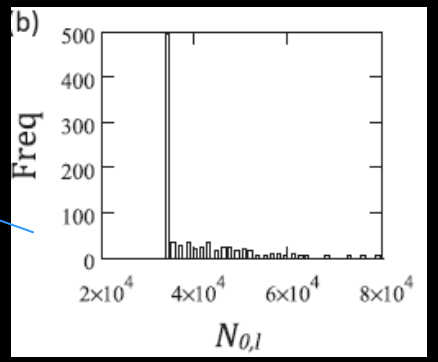
TCP modelling

$$\mathrm{BED} = D' = D\left(1 + \left(\frac{d}{\alpha/\beta}\right)\right) - \frac{0.692}{\alpha}\left(\frac{T - t_k}{t_p}\right)$$

Correction for OTT (median in study)

$$\mathrm{TCP}(D', \alpha, N_0) = \exp\left[-N_0 \exp\left(-\alpha D' - \frac{\alpha D'^2}{(\alpha/\beta)n}\right)\right]$$





More colonogenic cells in late than early stages

TCP modelling

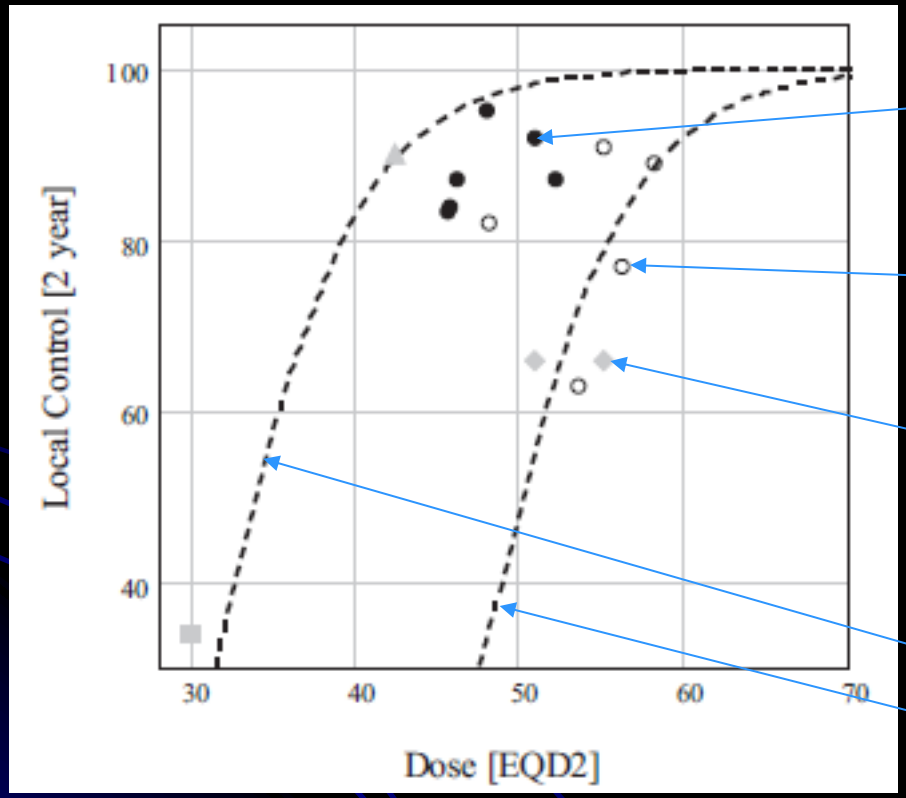
The proportions of early/late tumors used in the model

IMRT publications identified for use within the standard linear-quadratic model to create the TCP model.

		No. of patients	T1/T2 (%)	T3/4 (%)	Median dose delivered (Gy)	Median overall treatment time (days)	2 year local control unless stated (%)	FU median (months)
Milano et. al. [27]	2005	17	47.1	52.3	52.3	39*	82	20
Salama et al. [26]	2007	53	60.4	37.8	51.5	42	83.9 (18 months)	14.5
Pepek et al. [27]	2010	31	N/R	N/R	54.0	40*	100	19
Bazan et al. [28]	2011	29	72.4	27.6	54.0	40	92 (3 years)	32
Vieillot et al. [29]	2012	39	36.0	64.0	63.0	50	77	24
De Foe et al. [30]	2012	78	65.4	30.8	55.8	50	83.2	19.8
Dewas et al. [31]	2012	24	47.8	52.2	59.4	47	63	40
Kachnic et al. [32]	2012	43	67.0	14.0	52.2	39*	95	24
Deenen et al. [33]	2012	18	33.3	66.7	63.0	47*	89	28
Chuong et al. [34]	2013	52	55.8	44.2	56.0	38.5	90.8	19
Dasgupta et al. [35]	2013	45	64.3	31.2	54.0	40	87	27.5
Call et al. [36]	2014	148	72.0	28.0	51.3	40	87 (3 yrs)	26.8
Koerber et al. [37]	2014	68	69.1	30.9	54.5	37*	83	30.8

* Median overall treatment time not reported for the IMRT group therefore an estimation was calculated using dose/dose per fraction and interruptions.

TCP modelling



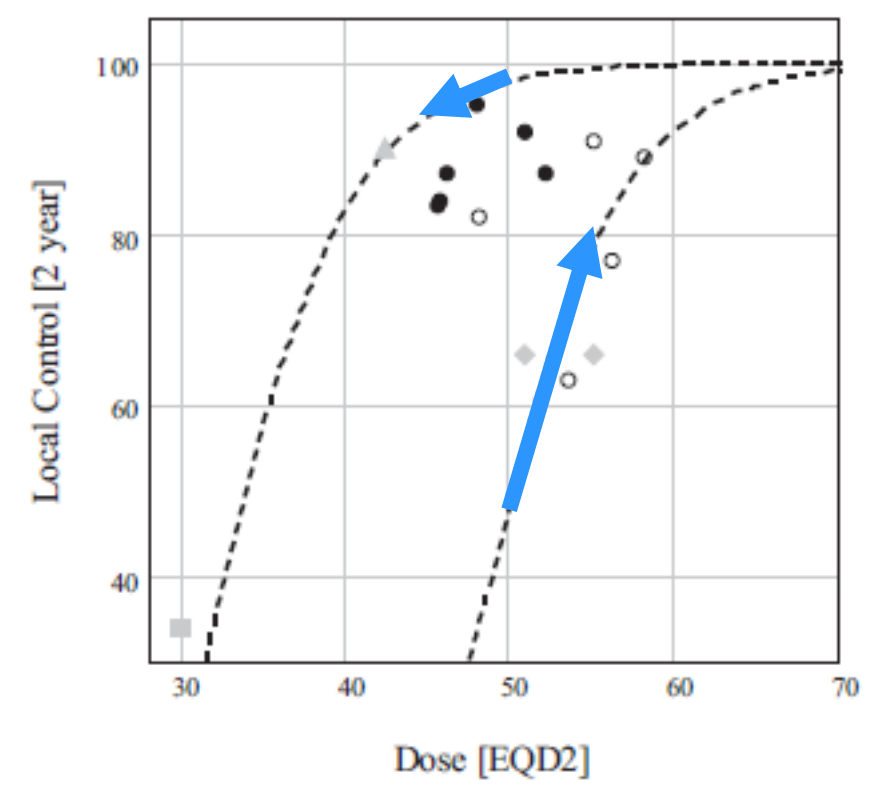
Series with >60% early stage (T1-2)

Series with <60% early stage (T1-2)

Validation series

Fittesd curves for:
Early stage (T1-2)
Late stage (T3+)

TCP modelling



Higher dose needed for late than for early stage

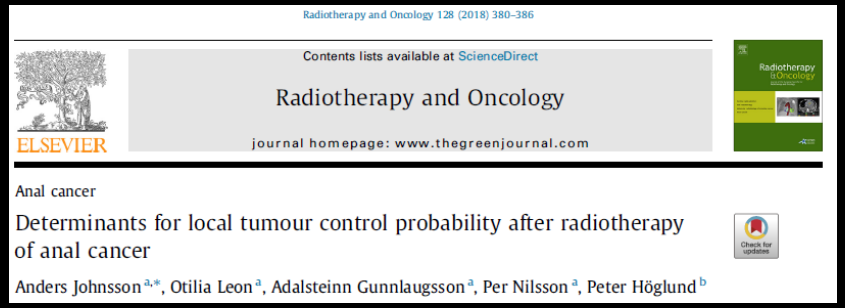
Early stage:
RT dose reduction from 50 Gy to 45 Gy reduces 2 year local control from 98% tio 95%

Late stage:
RT increase from 50 Gy to 55 Gy increases 2 year local control from 50% to 80%

NOAC database

- NOrdic Anal Cancer group
- Guidelines launched 2000
- 16 Oncology depts in Sweden, Norway and Denmark
- Outcome data collected 2008-10
- All patients diagnosed 1/7 2000 – 30/6 2007

Used for TCP analyses



Radiotherapy and Oncology 128 (2018) 380–386

Contents lists available at ScienceDirect

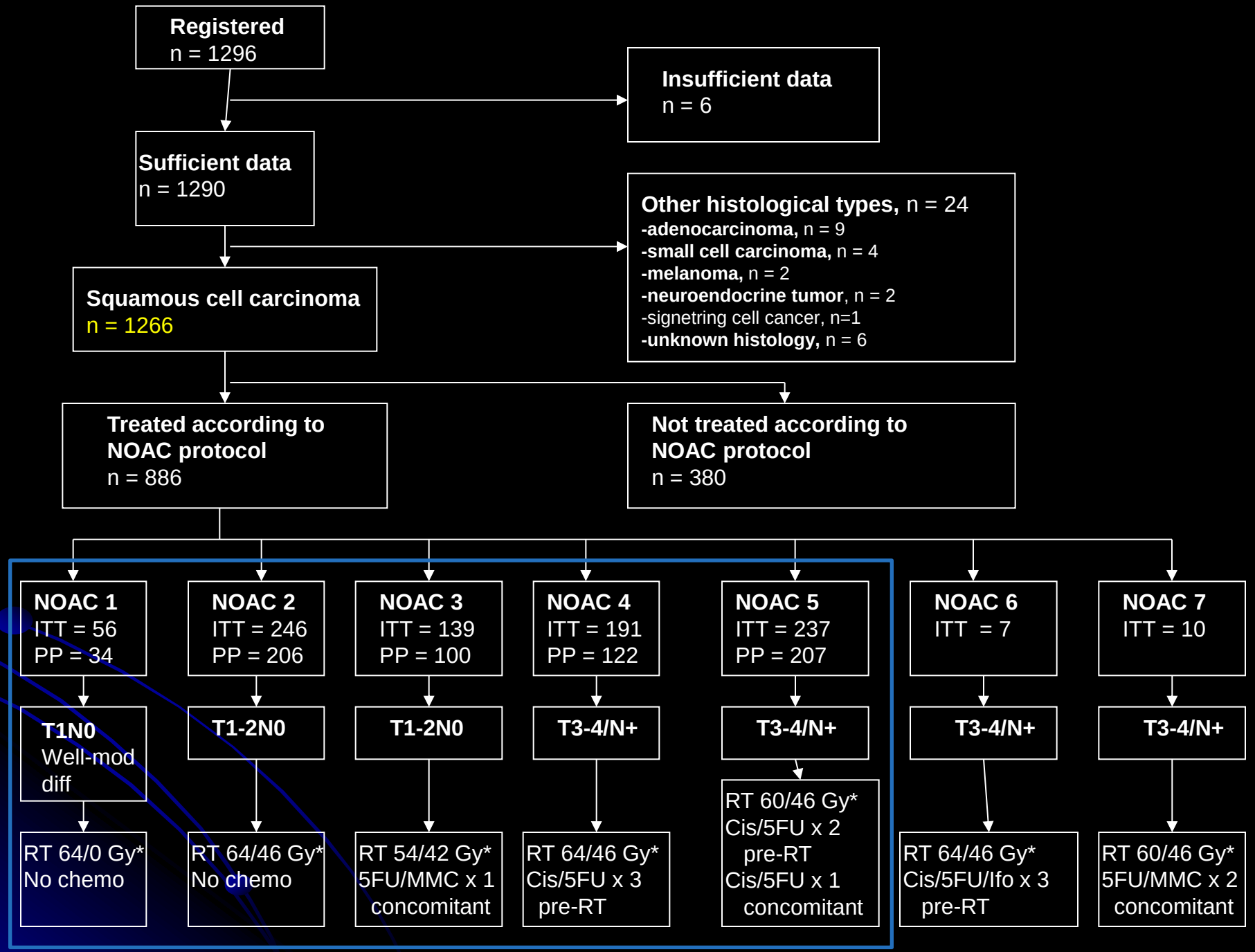
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

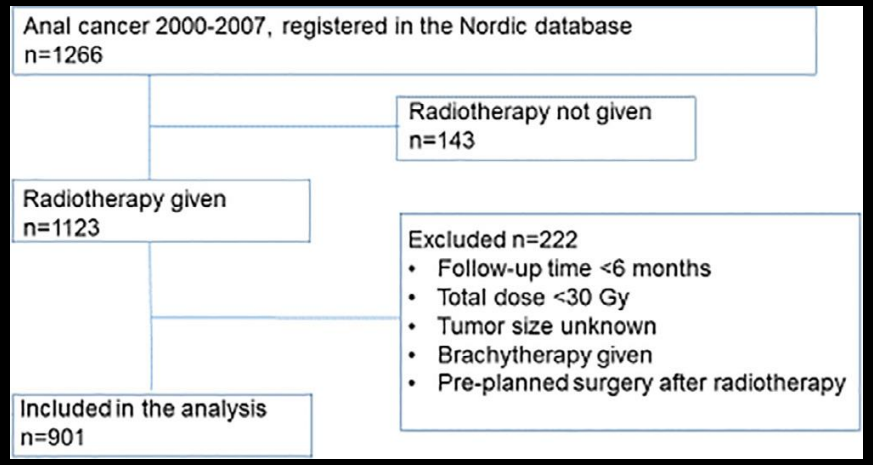
Anal cancer

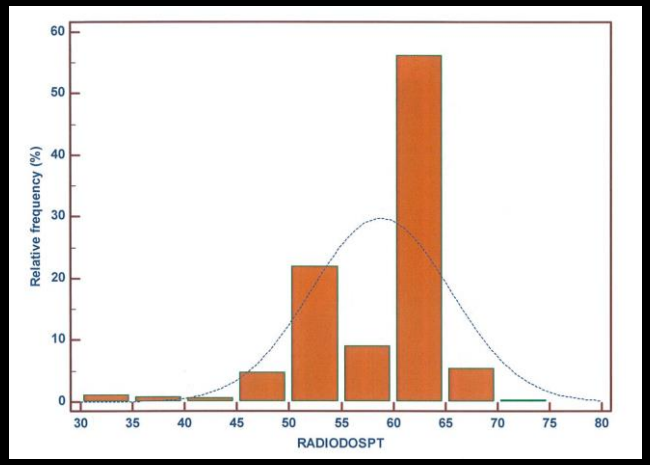
Determinants for local tumour control probability after radiotherapy of anal cancer

Anders Johnsson[a,*], Otilia Leon[a], Adalsteinn Gunnlaugsson[a], Per Nilsson[a], Peter Höglund[b]


Registered
n = 1296
Insufficient data
n = 6
Sufficient data
n = 1290
Other histological types, n = 24
-adenocarcinoma, n = 9
-small cell carcinoma, n = 4
-melanoma, n = 2
-neuroendocrine tumor, n = 2
-signetring cell cancer, n=1
-unknown histology, n = 6
Squamous cell carcinoma
n = 1266
Treated according to NOAC protocol
n = 886
Not treated according to NOAC protocol
n = 380
NOAC 1
ITT = 56
PP = 34
NOAC 2
ITT = 246
PP = 206
NOAC 3
ITT = 139
PP = 100
NOAC 4
ITT = 191
PP = 122
NOAC 5
ITT = 237
PP = 207
NOAC 6
ITT = 7
NOAC 7
ITT = 10
T1N0
Well-mod diff
T1-2N0
T1-2N0
T3-4/N+
T3-4/N+
T3-4/N+
T3-4/N+
RT 64/0 Gy*
No chemo
RT 64/46 Gy*
No chemo
RT 54/42 Gy*
5FU/MMC x 1
concomitant
RT 64/46 Gy*
Cis/5FU x 3
pre-RT
RT 60/46 Gy*
Cis/5FU x 2
pre-RT
Cis/5FU x 1
concomitant
RT 64/46 Gy*
Cis/5FU/Ifo x 3
pre-RT
RT 60/46 Gy*
5FU/MMC x 2
concomitant

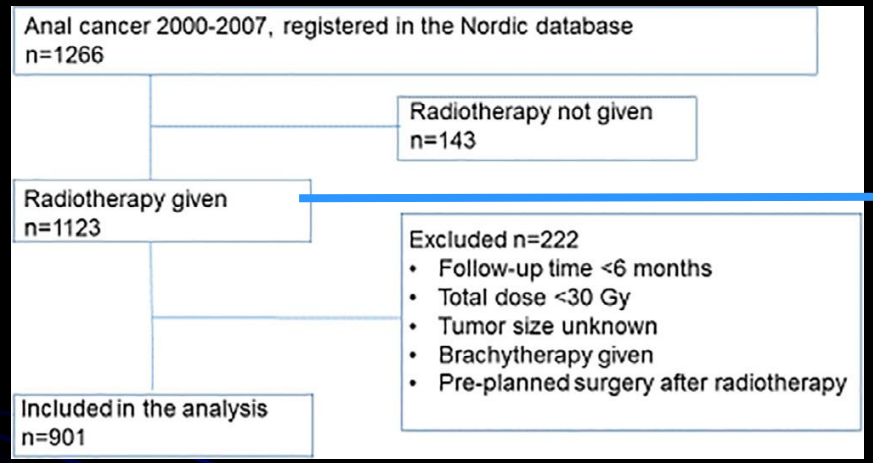
Local tumor control probability (LTCP)





Heterogenous RT doses
Advantage for LTCP modelling

Local tumor control probability (LTCP)



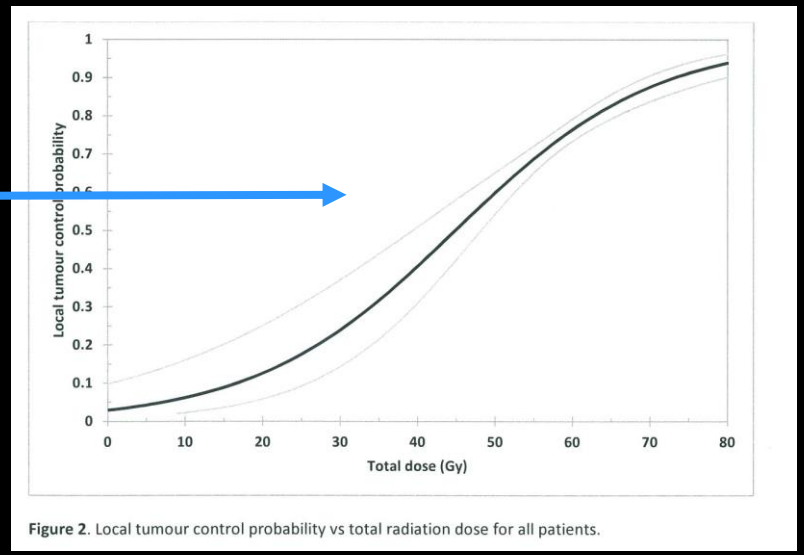
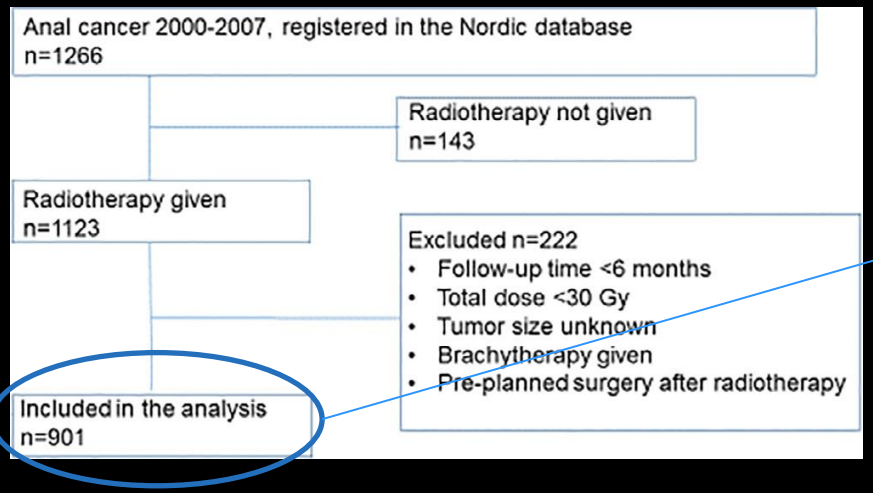


Figure 2. Local tumour control probability vs total radiation dose for all patients.

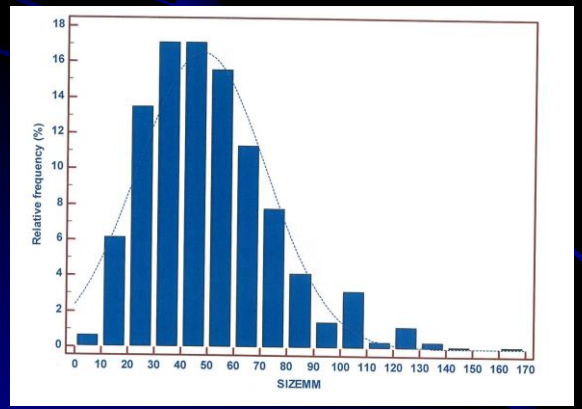
Nice LTCP curve among all RT patients – crude data

Determinants for local control after RT

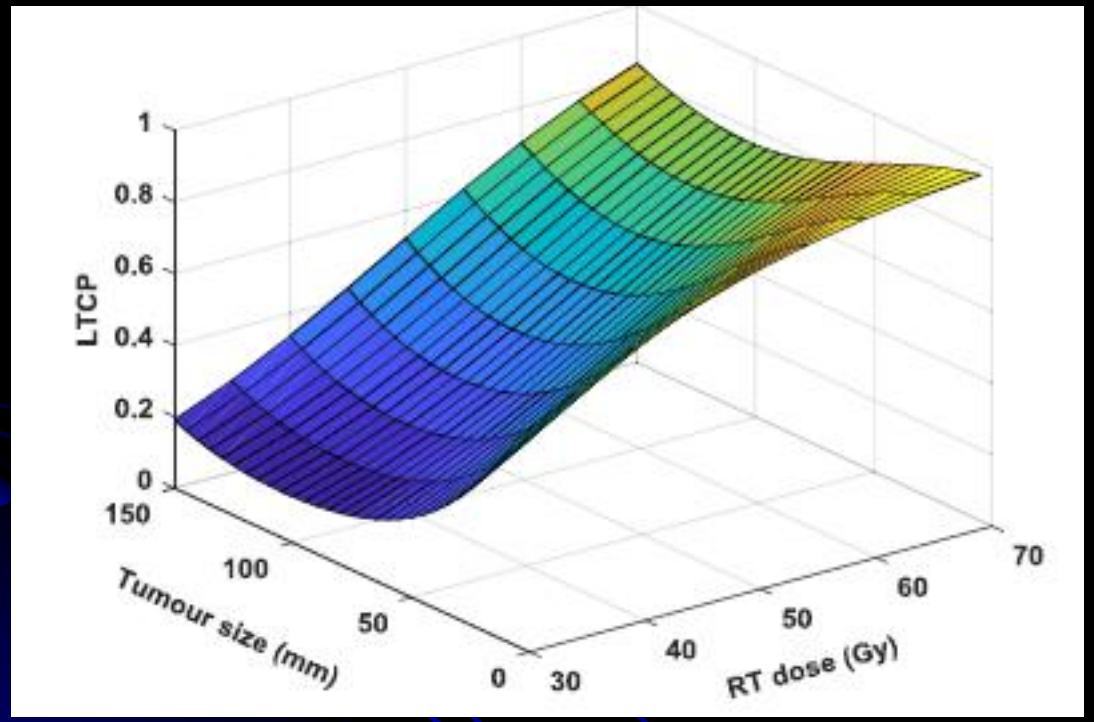


- Factors significantly influencing local failure (univariate)
  - RT dose
  - Tumor size
  - Gender
  - N stage
  - T4
  - Chemotherapy

Special focus on tumor size

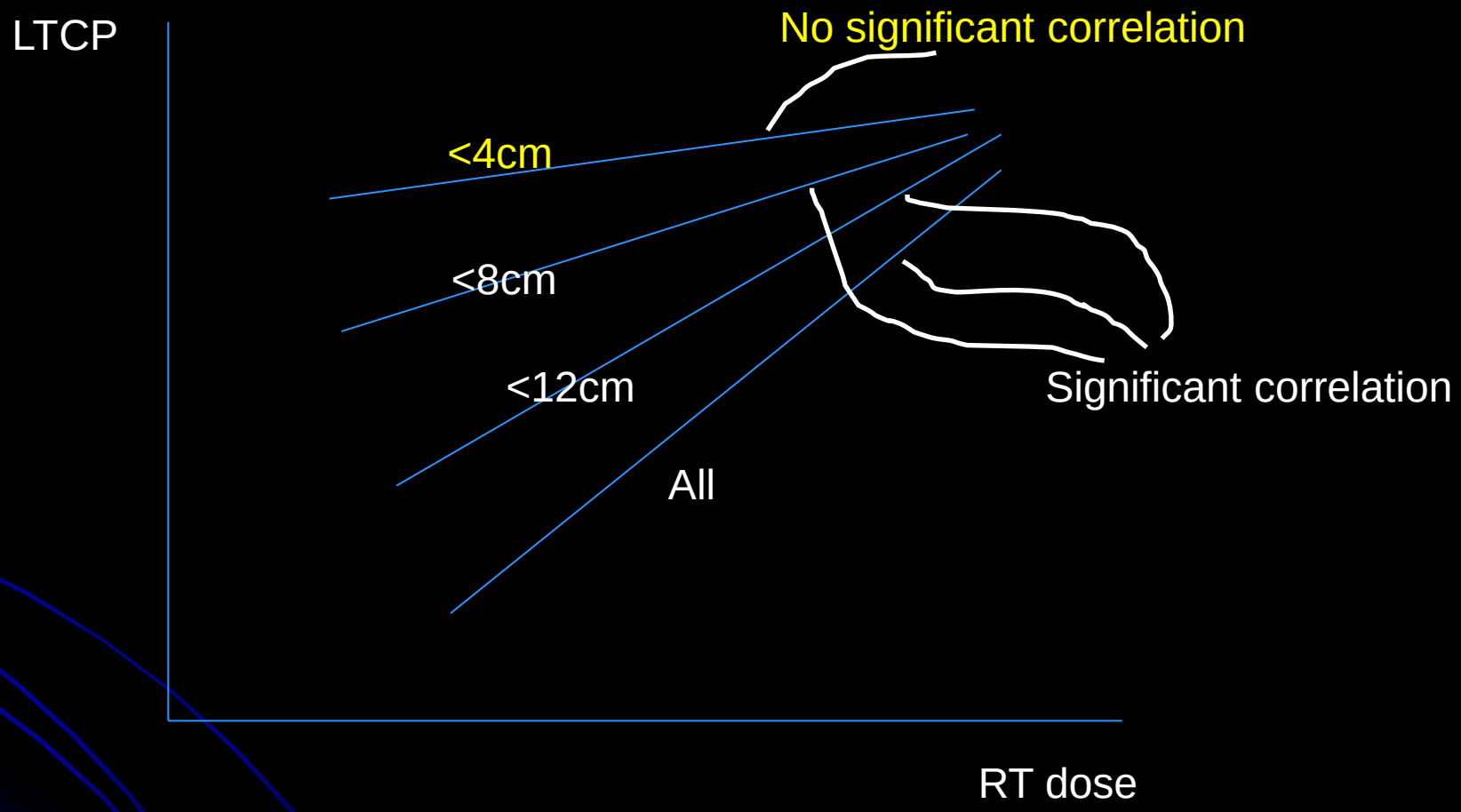


LTCP – RT dose – tumor size

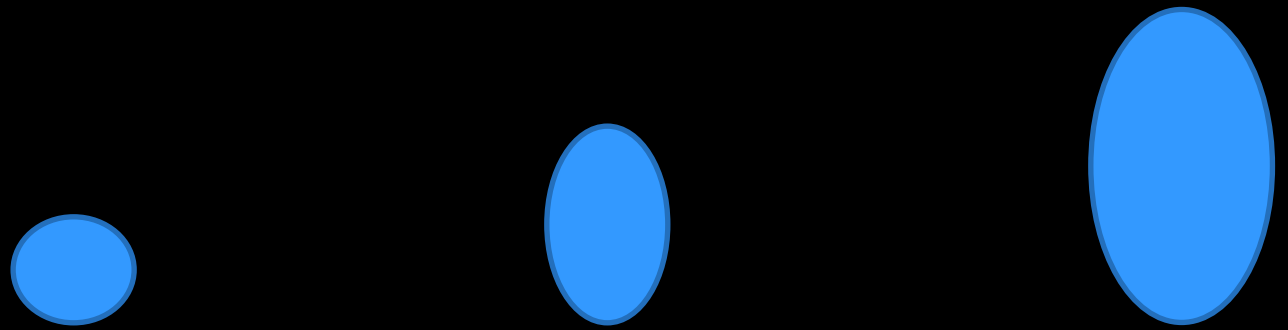


Non-linear relation
Paradoxical increase in LTCP for tumors >8 cm

LTCP by tumor size groups



Size groups in further analyses

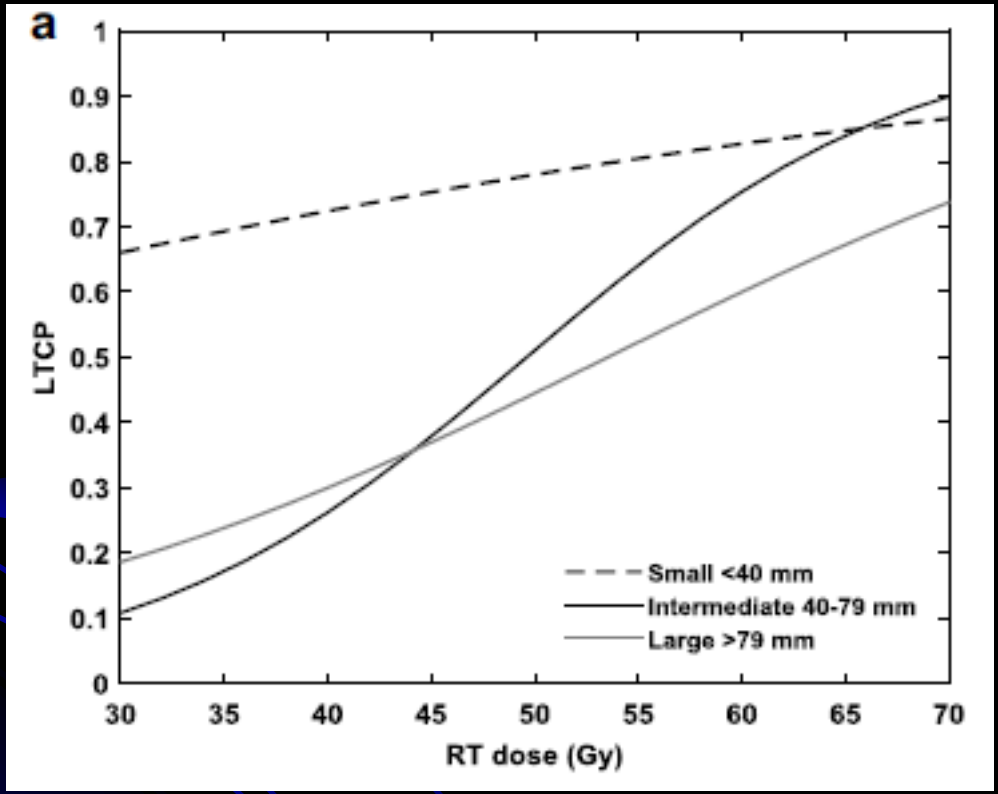


Small
<40 mm
n=337

Intermediate
40-79 mm
n=466

Large
≥80 mm
n=97

LTCP by size groups – univariable



RT dose more important for intermediate and large tumors

Busy table…

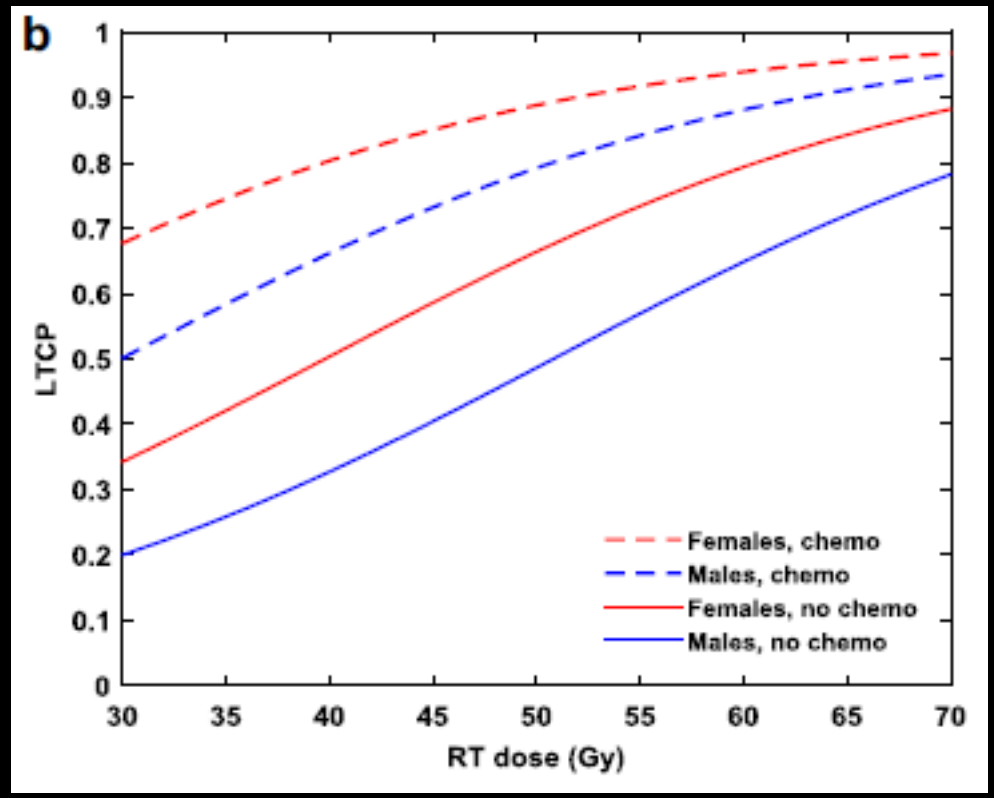
Univariable and multivariable predictors for local failure, divided into tumour size groups.

			Poisson regression						Logistic regression					
			Univariable			Multivariable			Univariable			Multivariable		
	n	*f*	RR	95% CI	*p*	RR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
	Tumour size <40 mm (number of patients $n = 338$, number of local failures $f = 60$)													
RT dose (Gy)	*64 (54–64)*[a]		0.97	0.93–1.01	0.142	0.91	0.88–0.94	<0.001	0.97	0.93–1.01	0.146	0.94	0.89–0.98	0.005
Female gender	*254*	*37*	0.45	0.27–0.76	0.002	0.42	0.25–0.72	0.001	0.45	0.25–0.83	0.009	0.48	0.26–0.90	0.020
T4	*14*	*3*	1.23	0.30–3.34	0.722				1.28	0.28–4.25	0.714			
N+	*45*	*8*	1.08	0.47–2.14	0.841				1.00	0.41–2.18	0.996			
Chemotherapy	*134*	*14*	0.36	0.19–0.64	0.001	0.17	0.09–0.32	<0.001	0.40	0.20–0.75	0.005	0.25	0.11–0.50	<0.001
	Tumour size 40–79 mm ($n = 465$, $f = 132$)													
RT dose (Gy)	*60 (56–64)*[b]		0.90	0.88–0.92	<0.001	0.90	0.88–0.92	<0.001	0.90	0.87–0.93	<0.001	0.89	0.86–0.92	<0.001
Female gender	*336*	*85*	0.57	0.40–0.82	0.002	0.48	0.33–0.69	<0.001	0.59	0.38–0.92	0.018	0.46	0.29–0.74	0.001
T4	*94*	*35*	1.57	1.05–2.28	0.023	1.68	1.11–2.48	0.011	1.68	1.03–2.69	0.034	1.74	1.03–2.91	0.037
N+	*191*	*65*	1.65	1.18–2.33	0.004	2.43	1.69–3.49	<0.001	1.59	1.06–2.40	0.025	1.83	1.16–2.89	0.010
Chemotherapy	*339*	*91*	0.58	0.40–0.84	0.003	0.45	0.31–0.67	<0.001	0.76	0.49–1.19	0.227	0.55	0.33–0.93	0.025
	Tumour size >79 mm ($n = 98$, $f = 44$)													
RT dose (Gy)	*60 (54–60)*[c]		0.92	0.88–0.96	<0.001	0.91	0.86–0.95	<0.001	0.94	0.88–0.99	0.038	0.94	0.88–1.00	0.044
Female gender	*63*	*23*	0.36	0.20–0.66	0.001	0.30	0.16–0.55	<0.001	0.38	0.16–0.89	0.027	0.38	0.16–0.91	0.031
T4	*58*	*29*	1.82	0.99–3.48	0.060				1.67	0.74–3.84	0.223			
N+	*61*	*29*	1.54	0.84–2.95	0.174				1.33	0.58–3.07	0.500			
Chemotherapy	*83*	*37*	0.81	0.38–1.98	0.604				0.92	0.30–2.85	0.881			

[a,b,c] Median (IQR); range 30–68[a], 30–70[b] and 30–70[c].

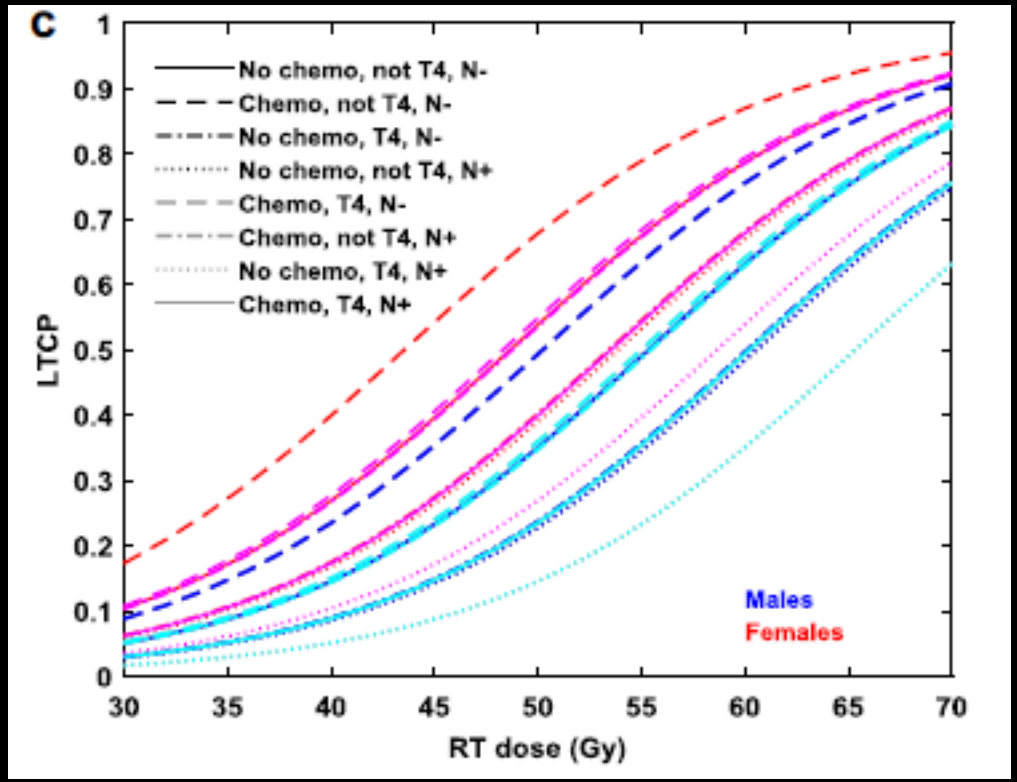
Small tumors (<40 mm)

N=337	Univariable	Multivariable
RT dose	P=0,1	P=0,005
Gender	P=0,009	P=0,02
T4	P=0,7	
N+	P=1,0	
Chemotherapy	P=0,005	P<0,001



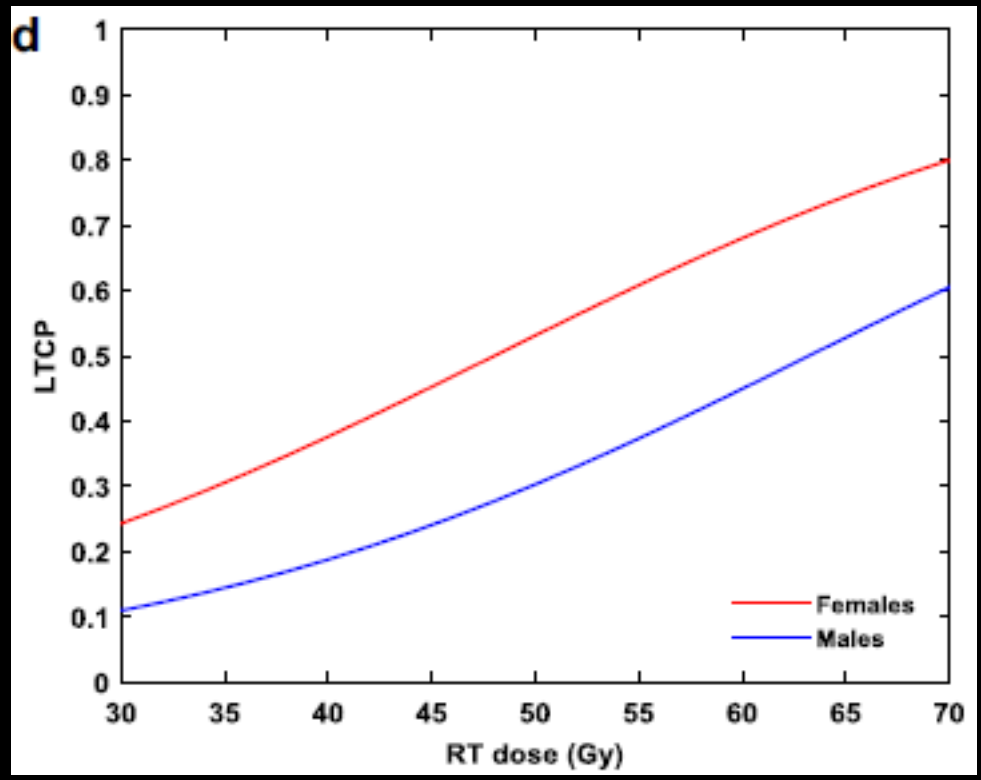
Intermediate tumors (40-79 mm)

N=465	Univariable	Multivariable
RT dose	P<0,001	P<0,001
Gender	P=0,02	P=0,001
T4	P=0,03	P=0,04
N+	P=0,03	P=0,01
Chemotherapy	P=0,2	P=0,03



Large tumors (>79 mm)

N=98	Univariable	Multivariable
RT dose	P<0,001	P<0,001
Gender	P=0,02	P=0,001
T4	P=0,2	
N+	P=0,5	
Chemotherapy	P=0,9	



General conclusions

- Tumors <4cm – lower RT dose
- T4 (regardless of size) – higher RT dose
- N+ higher RT dose
- Add chemotherapy

General conclusions

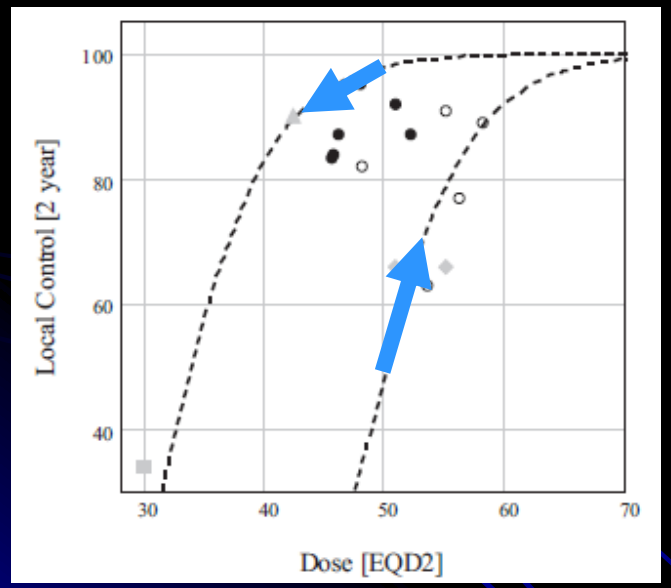
- Tumors < 4cm – lower RT dose
- T4 (regardless of size) – higher RT dose
- N+ higher RT dose
- Add chemotherapy

We already do this – our results fit with guidelines

	Muirhead	Johnsson
Pat #	645	901
Individual patient data	No	Yes
IMRT	Yes	No

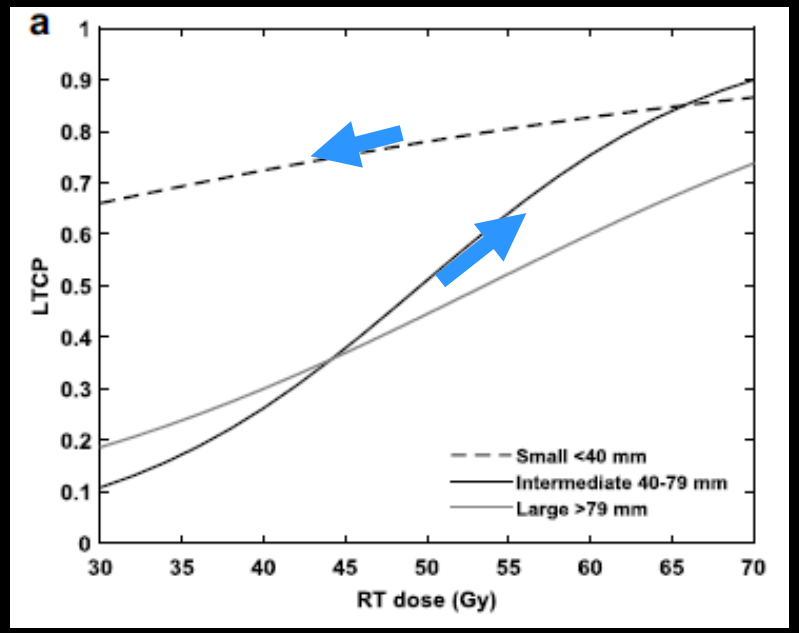
Interstudy comparison

Muirhead



Steeper TCP curves

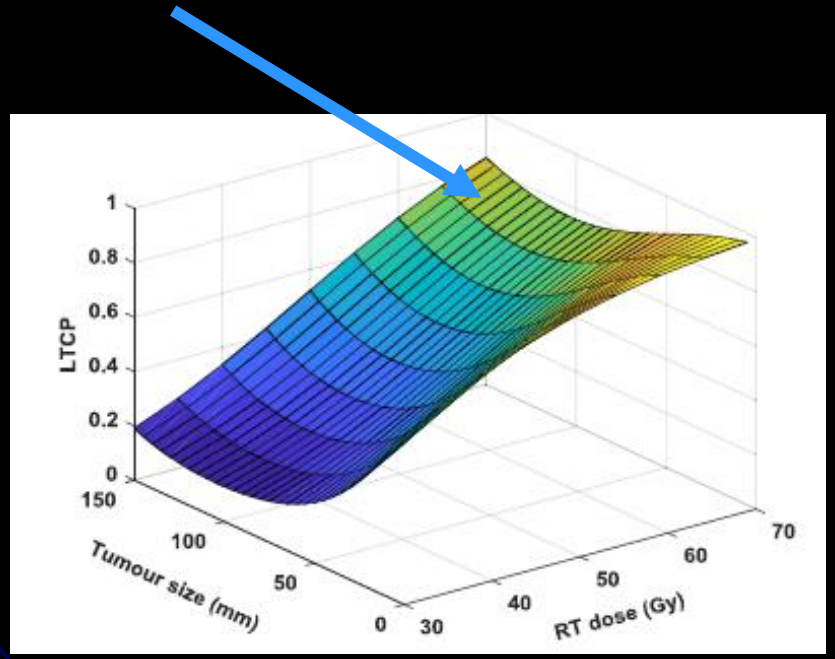
Johnsson



- General conclusions similar
- Different tumor size groups
- Slightly different endpoints
- Muirhead: No low-dose data
- Our data more reliable due to ”real” data and not modelled…?

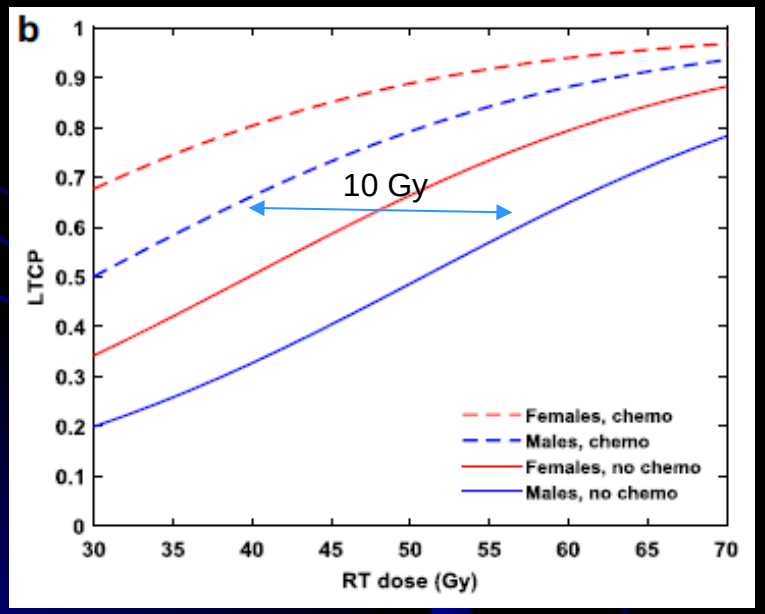
General conclusions

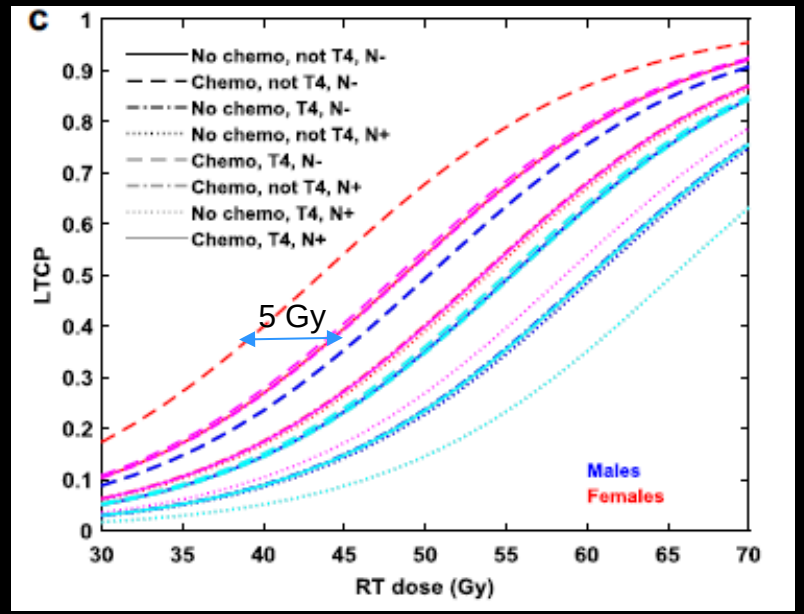
- Do not disqualify very large tumors from optimal treatment with curative intent!



Further thoughts

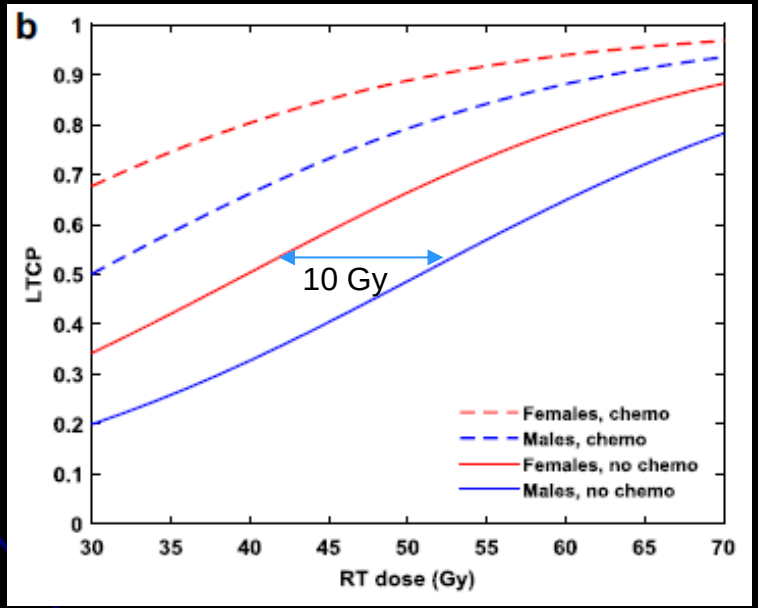
- Increase the RT dose by 5 -10 Gy if chemotherapy cannot be given





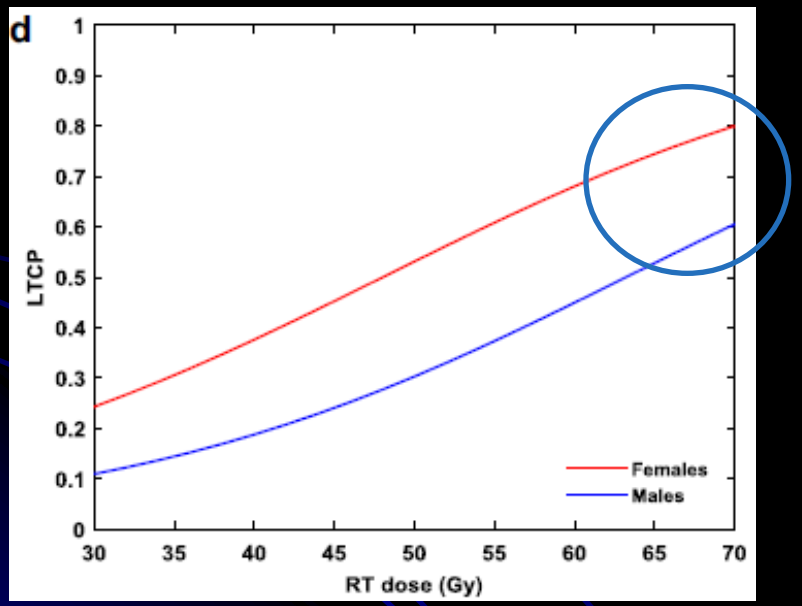
Further thoughts

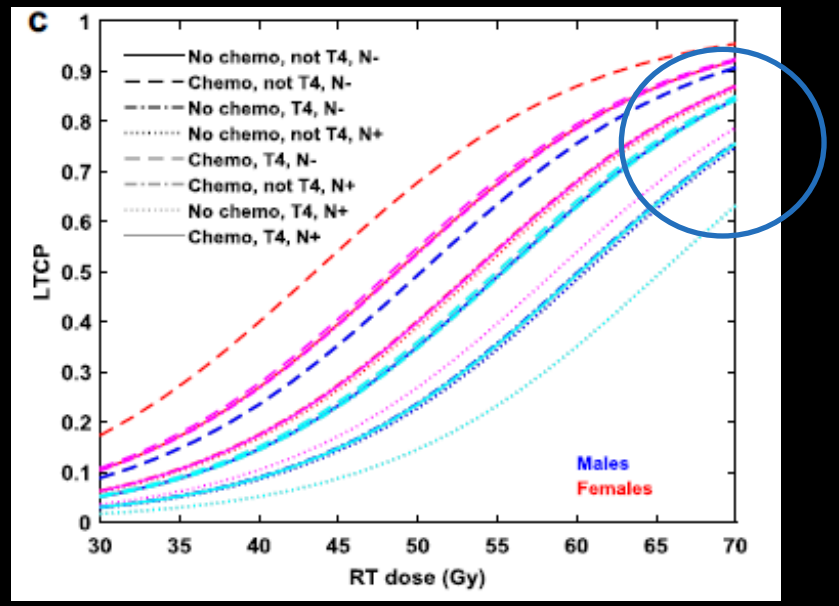
- Should we increase the RT dose by 10 Gy in male patients??



Further thoughts

- Role for RT dose escalation >60 Gy after all ??





Thank You