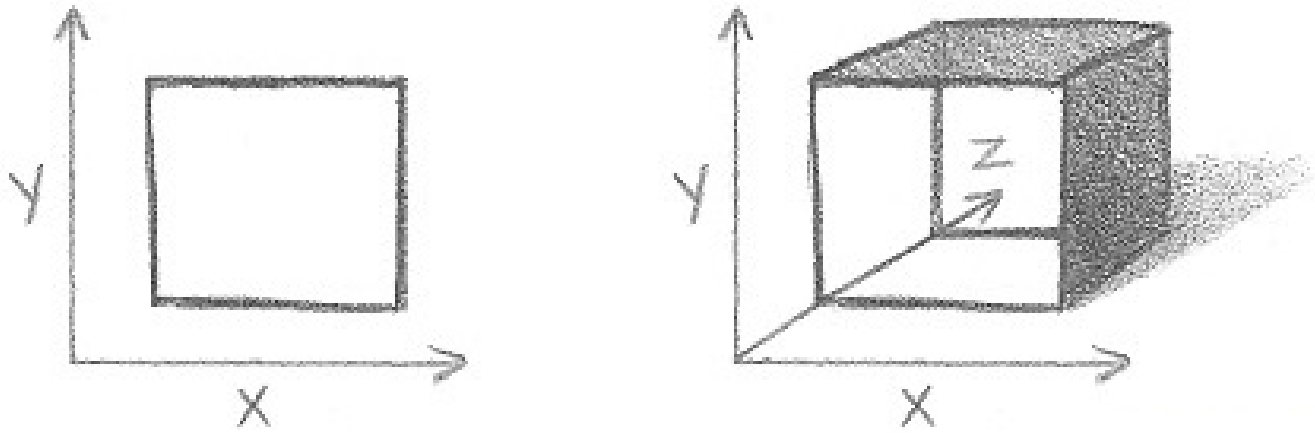
From 2D to 3D: Learned clinical needs for modern treatments

PROF. DR. KARIN HAUSTERMANS

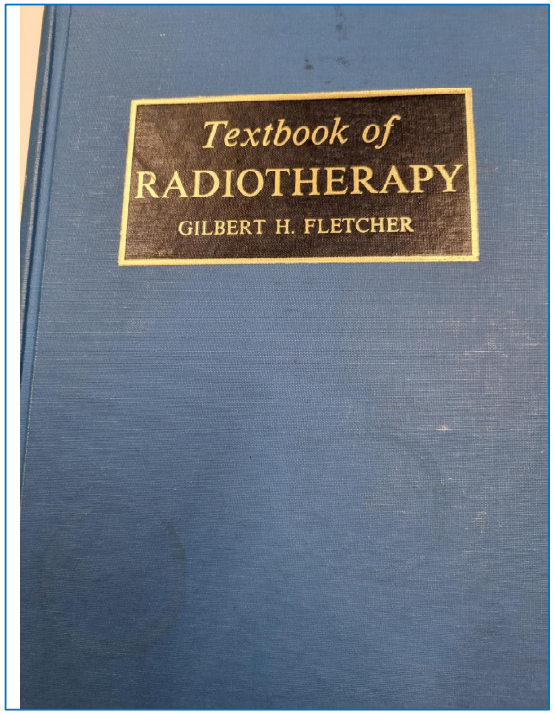
UZ LEUVEN, BELGIUM

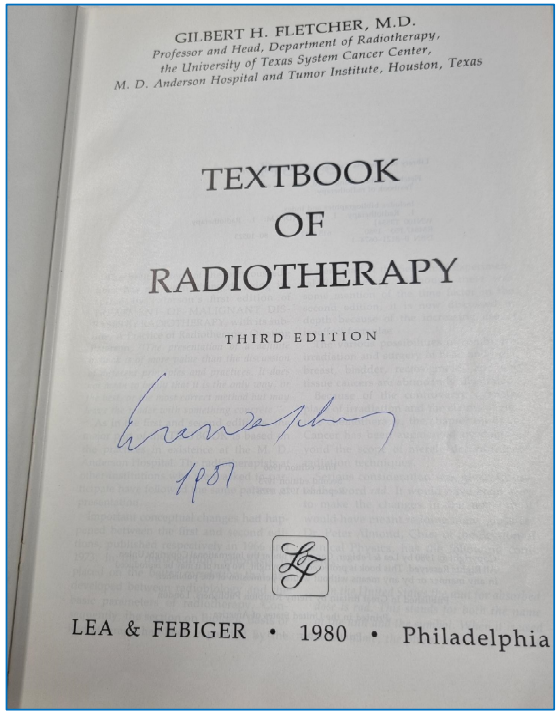


From 2D to 3D…

BACK TO THE FUTURE

A source of inspiration…



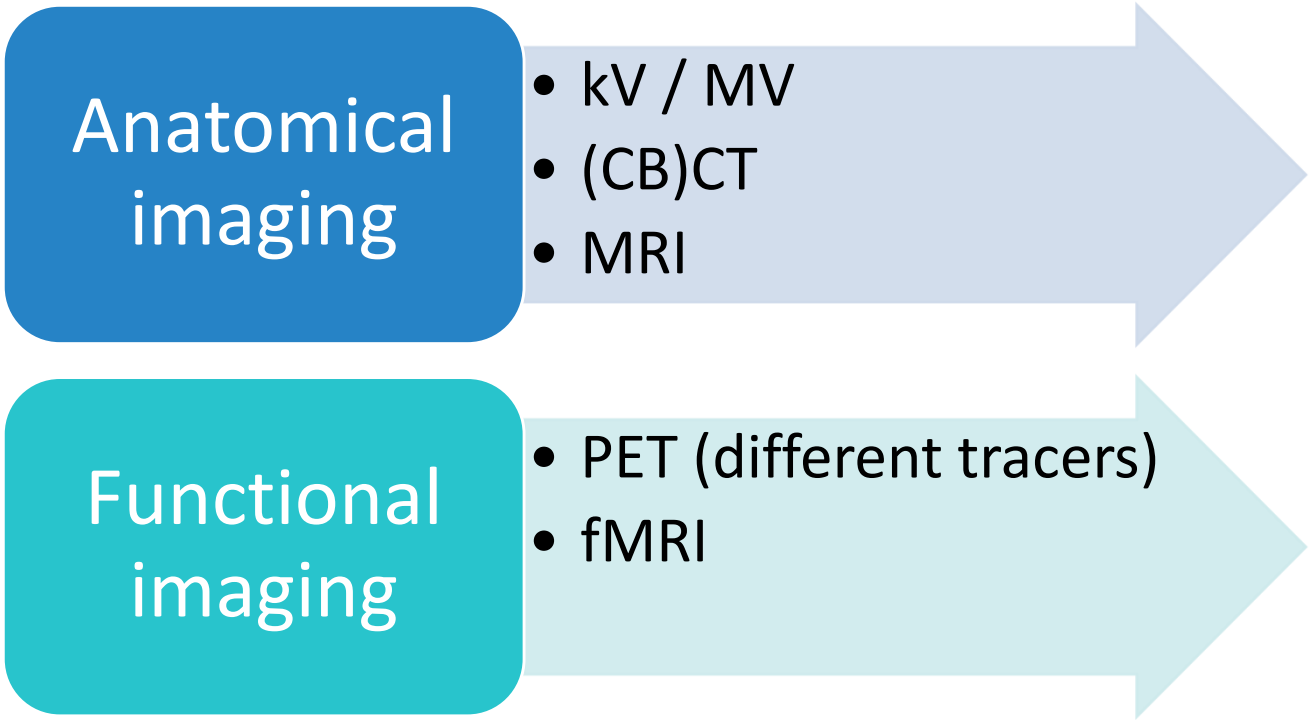


Learned clinical needs #1

We need accurate 3D image information
to define and delineate the target and to avoid the OAR

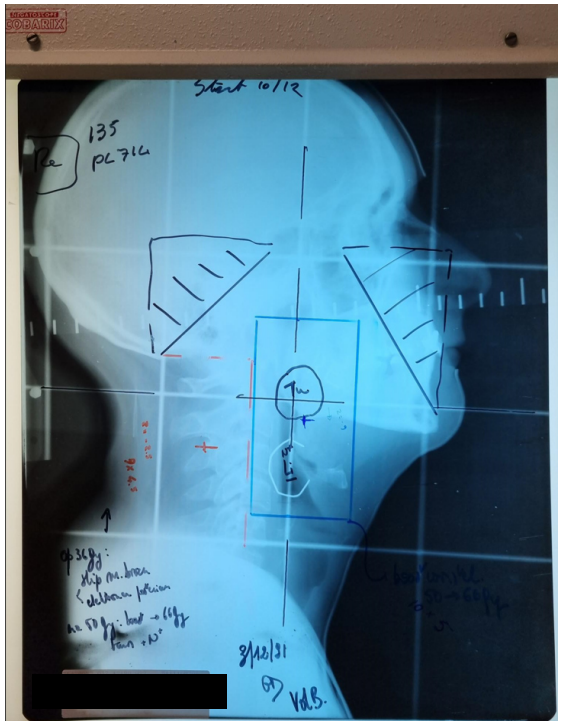
Imaging: from 2D to 3D

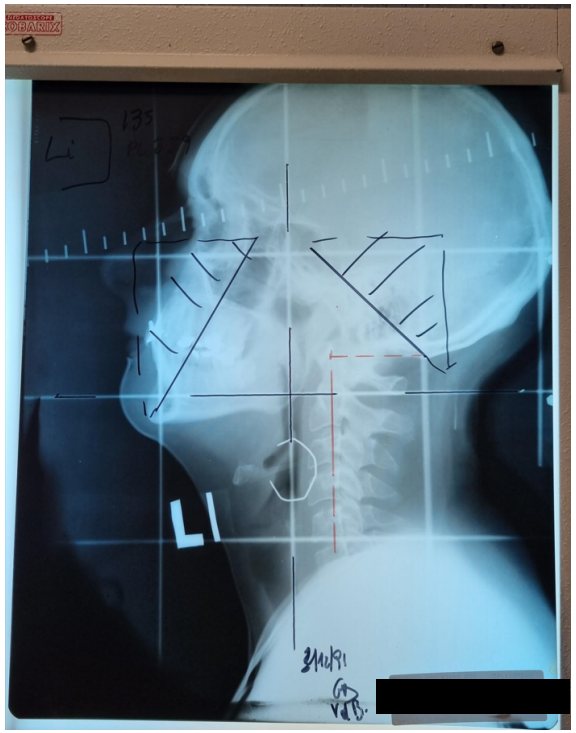
Imaging modalities



Imaging: from 2D to 3D

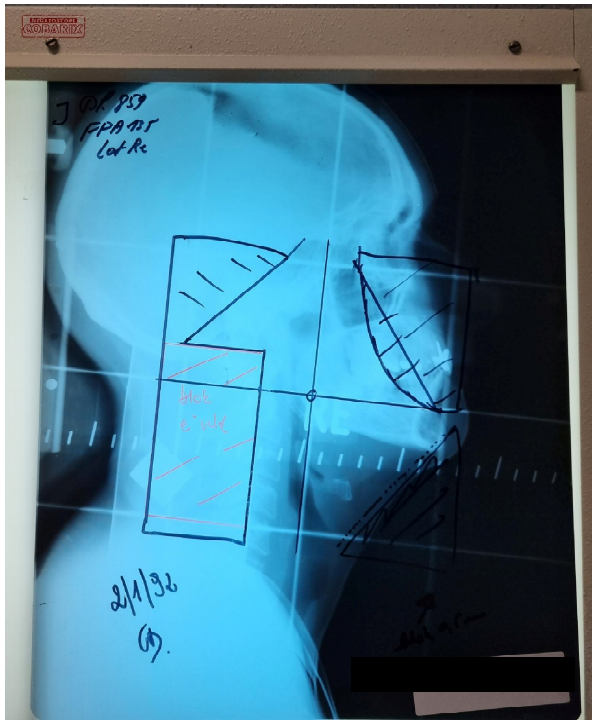
Case #1

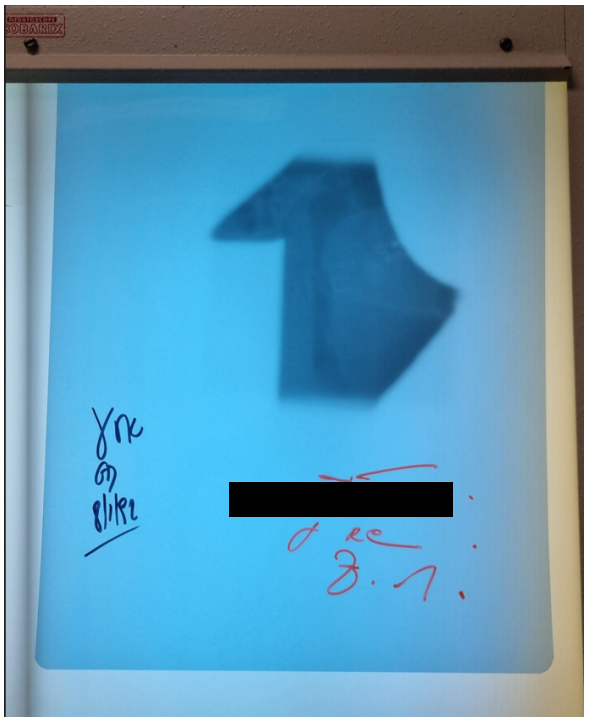




Imaging: from 2D to 3D

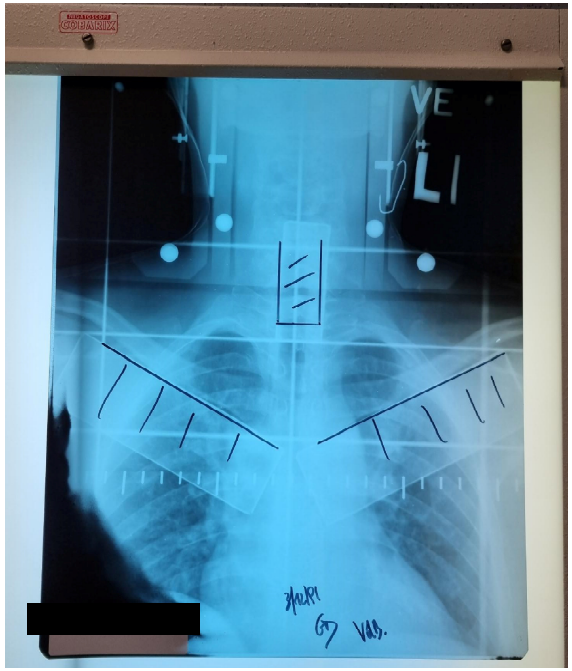
Case #1

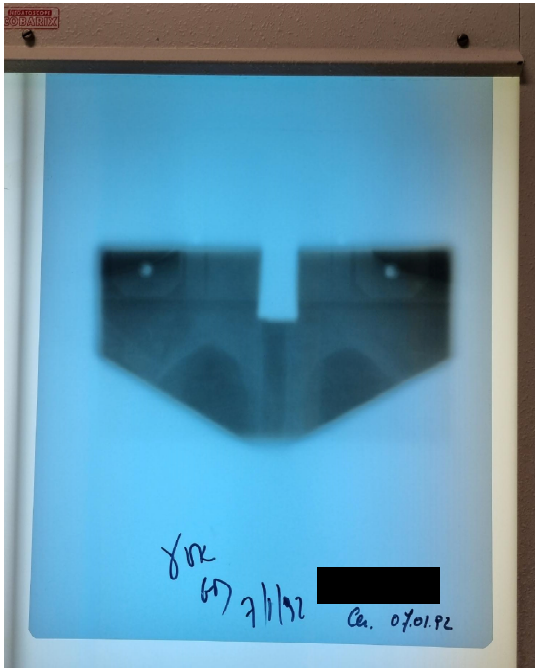




Imaging: from 2D to 3D

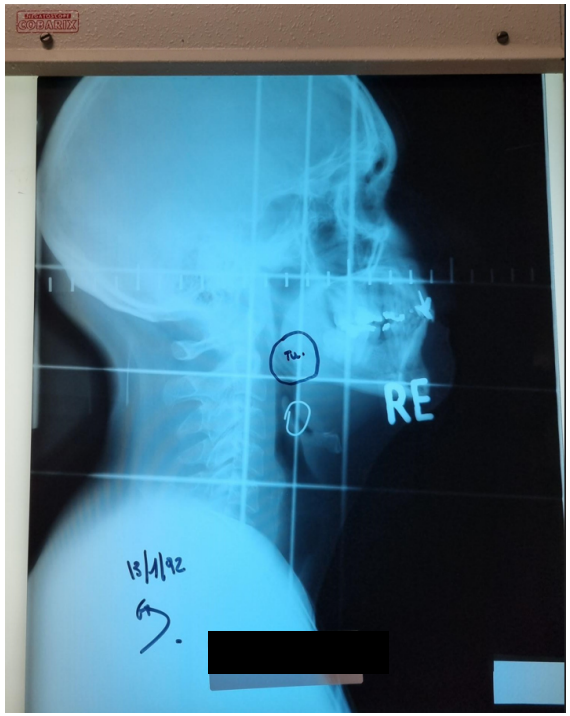
Case #1

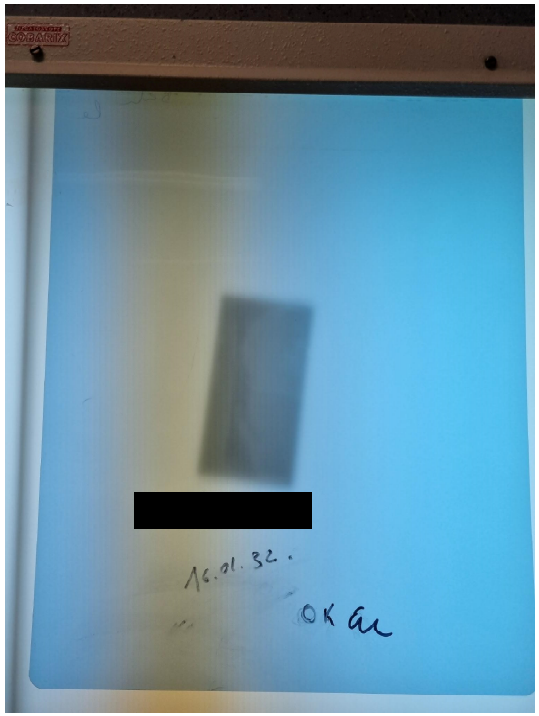




Imaging: from 2D to 3D

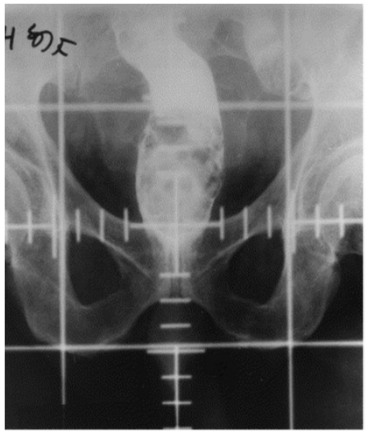
Case #1

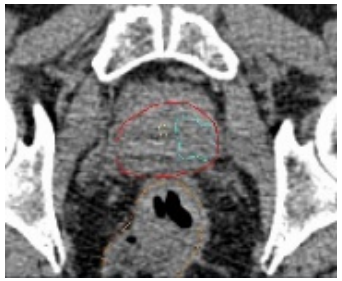


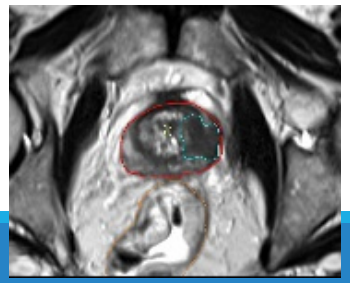


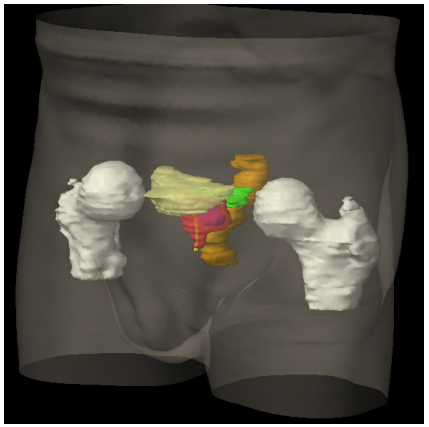
Imaging: from 2D to 3D

Bony anatomy
&
Hand-drawn
blocks







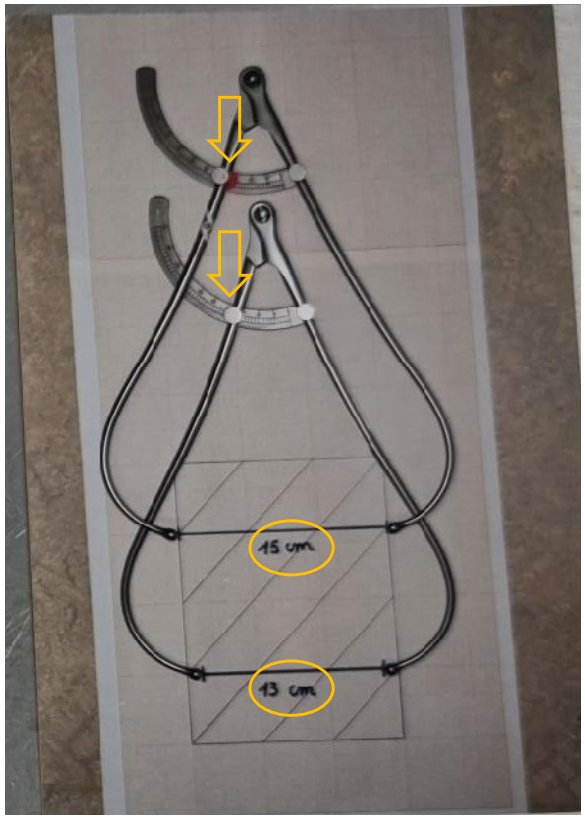


3D imaging and
target delineation

Learned clinical needs #2

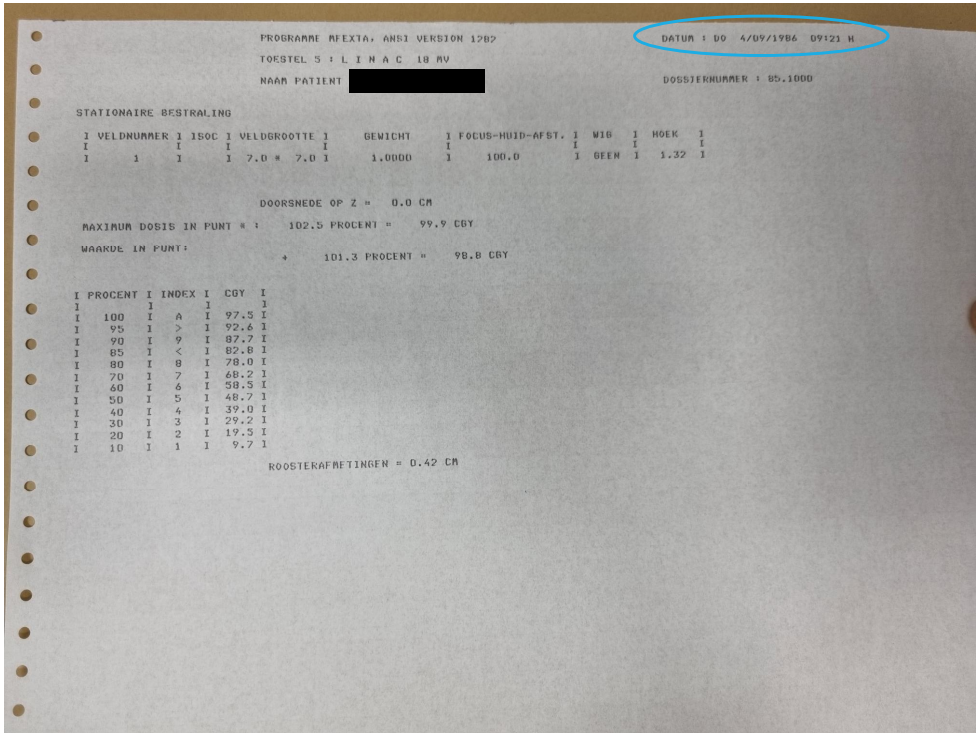
We need powerful dose calculation algorithms
to accurately determine the dose to be delivered

From 2D to 3D: treatment plan



From 2D to 3D: treatment plan

1986!



PROGRAMME MEEXTA, ANSI VERSION 1982 DATUM : DO 4/09/1986 09:21 H

TOESTEL 5 : L I N A C 18 MV

NAAM PATIENT [redacted] DOSSIERNUMMER : 85.1000

STATIONAIRE BESTRALING

VELDNUMMER	ISOC	VELDGROOTTE	GEWICHT	FOCUS-HUID-AFST.	WIG	HOEK
1	1	7.0 * 7.0	1.0000	100.0	GEEN	1.32

DOORSNEDE OP Z = 0.0 CM

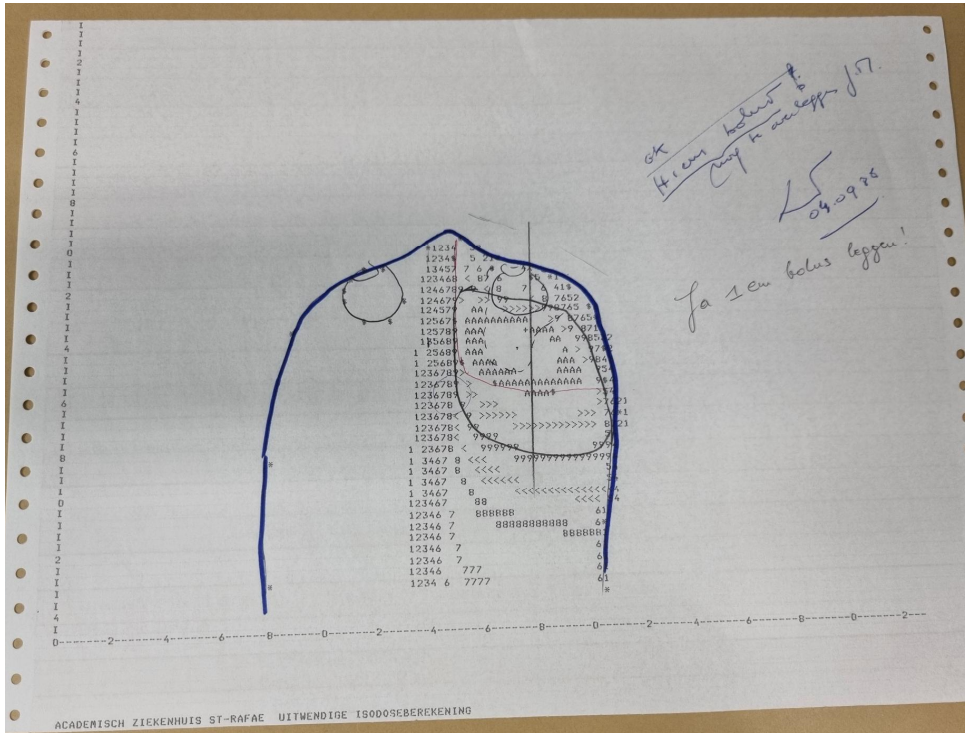
MAXIMUM DOSIS IN PUNT * : 102.5 PROCENT = 99.9 CGY

WAARDE IN PUNT:

+ 101.3 PROCENT = 98.8 CGY

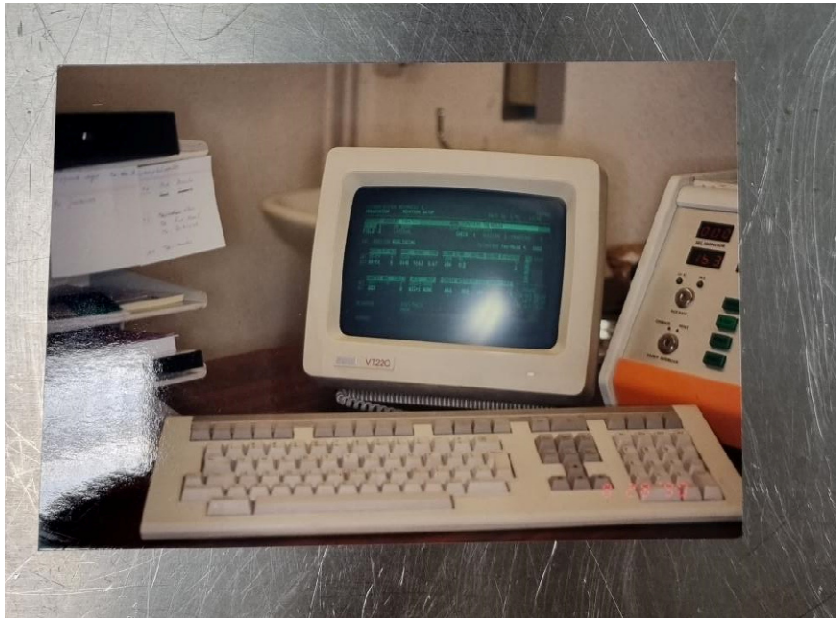
PROCENT	INDEX	CGY
100	A	97.5
95	>	92.6
90	9	87.7
85	<	82.8
80	8	78.0
70	7	68.2
60	6	58.5
50	5	48.7
40	4	39.0
30	3	29.2
20	2	19.5
10	1	9.7

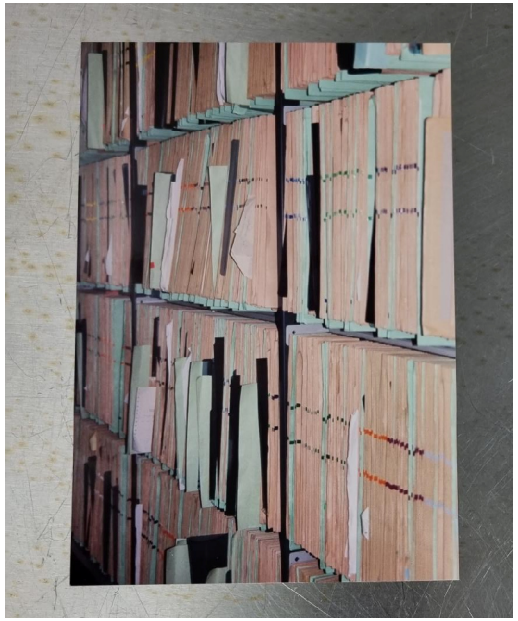
ROOSTERAFMETINGEN = 0.42 CM



ACADEMISCH ZIEKENHUIS ST-RAFAE UITWENDIGE ISODOSEBEREKENING

From 2D to 3D: treatment plan



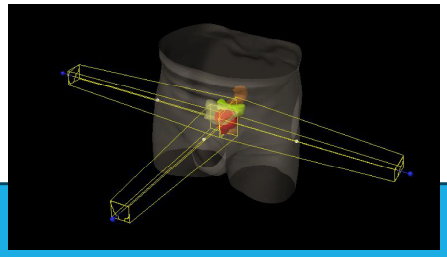


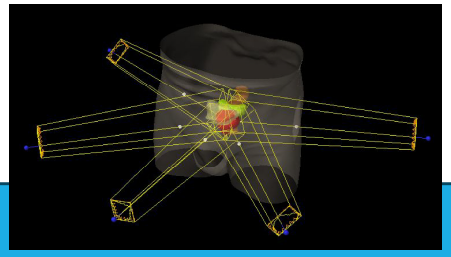
From 2D to 3D: treatment plan

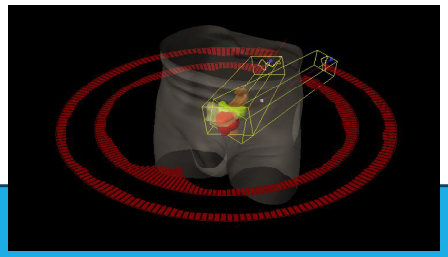
Collimation

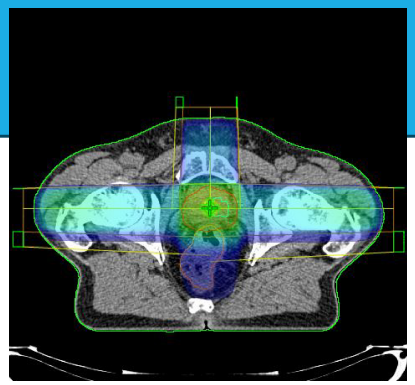
Intensity modulation

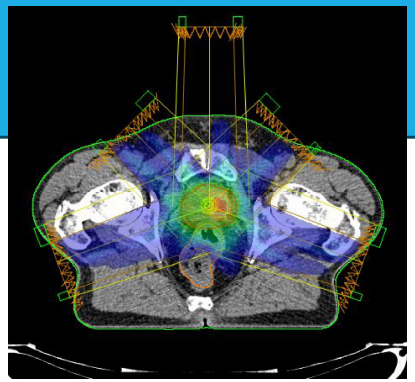
Dynamic arc therapy

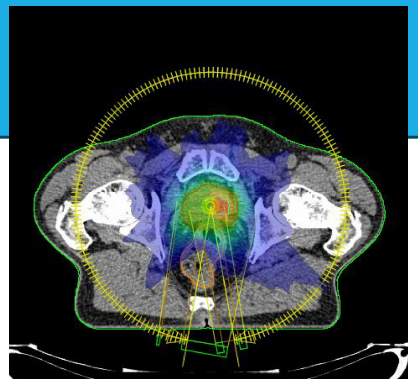


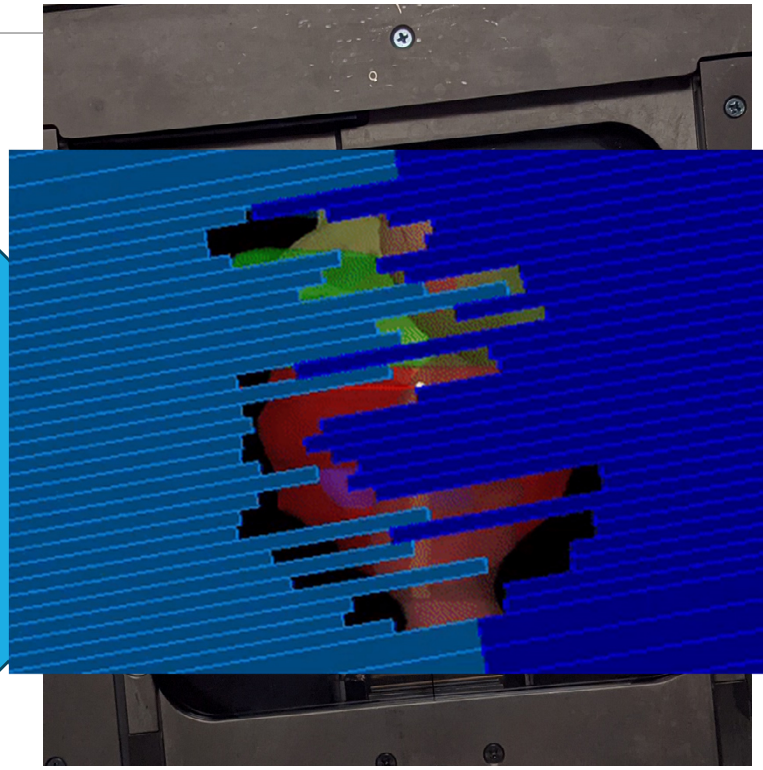










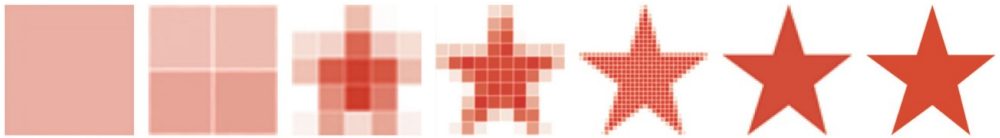


Learned clinical needs #3

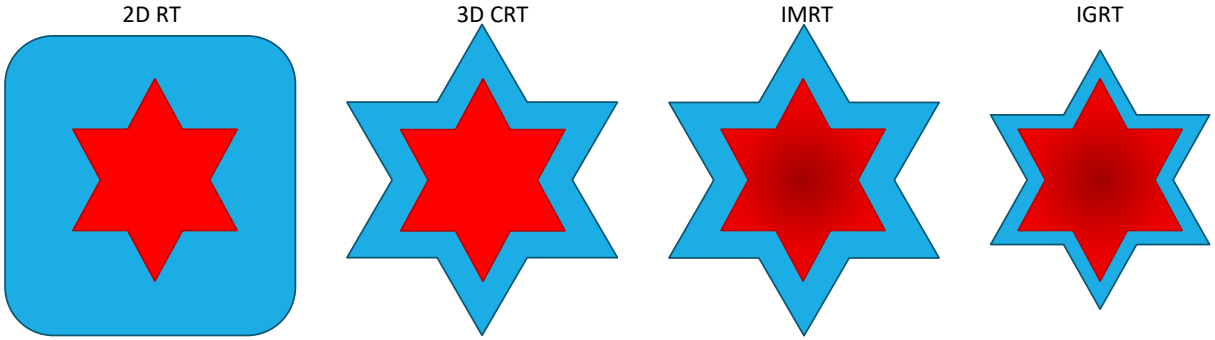
We need the right radiation technology
to deliver the correct 3D dose distribution

Technological evolution

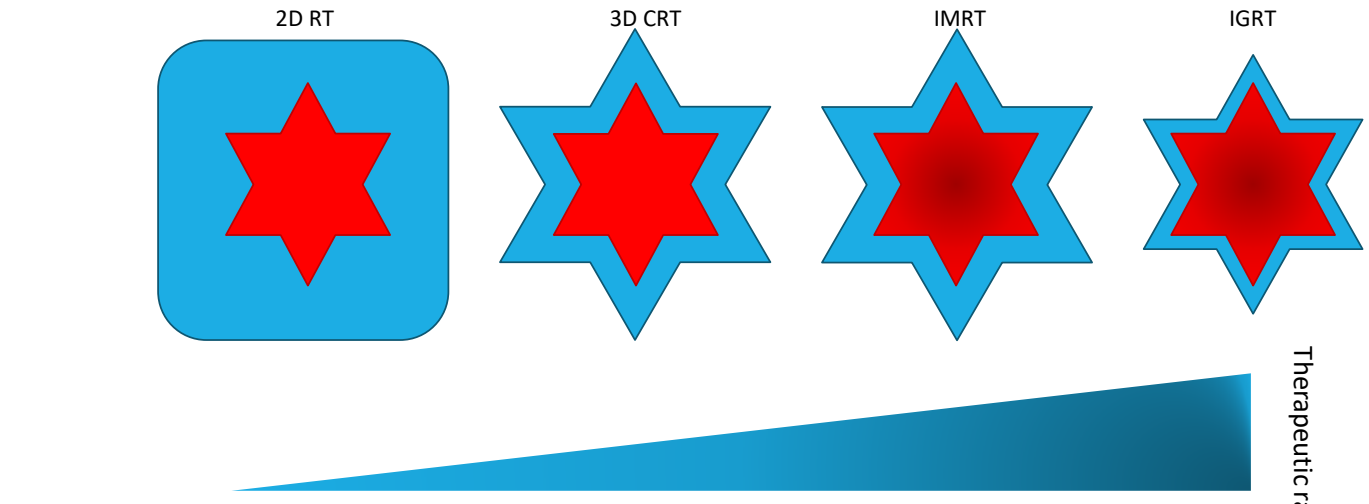
Imaging



RT delivery techniques

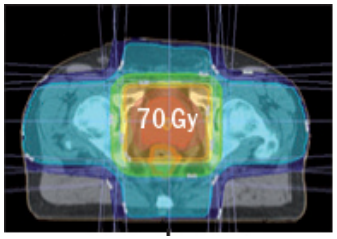


Technological evolution



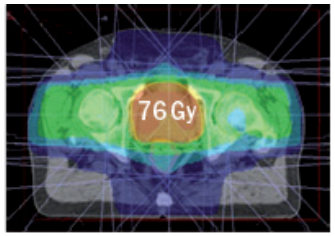
From 2D to 3D: conventional vs conformal

CONVENTIONAL RT



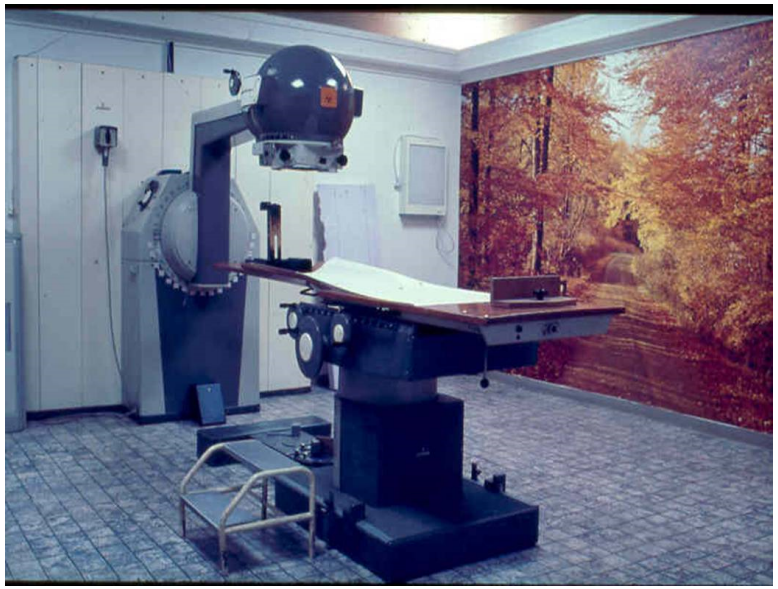
- 2D treatment planning
- Large safety margins
- Inadequate shielding of normal tissues

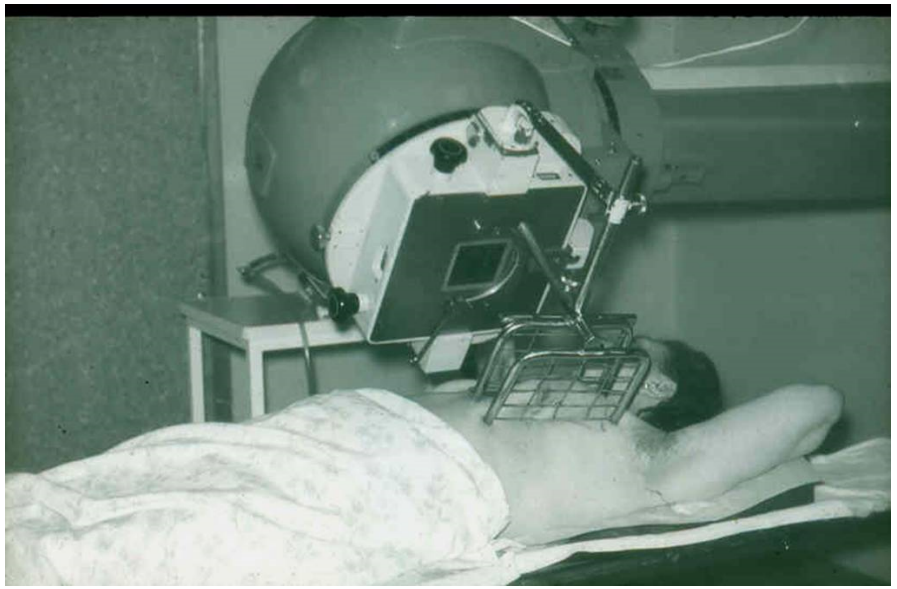
3D-CONFORMAL RT



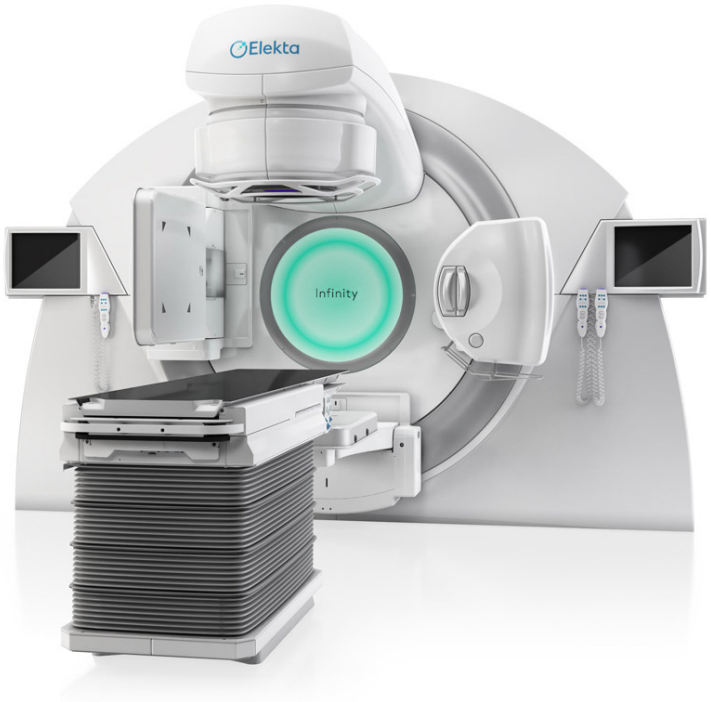
- CT-based 3D treatment planning
- Computer-controlled RT delivery
- Better shaping of individual beams to conform shape and size of target volume
- Reduced normal tissue volume exposed to high radiation dose levels

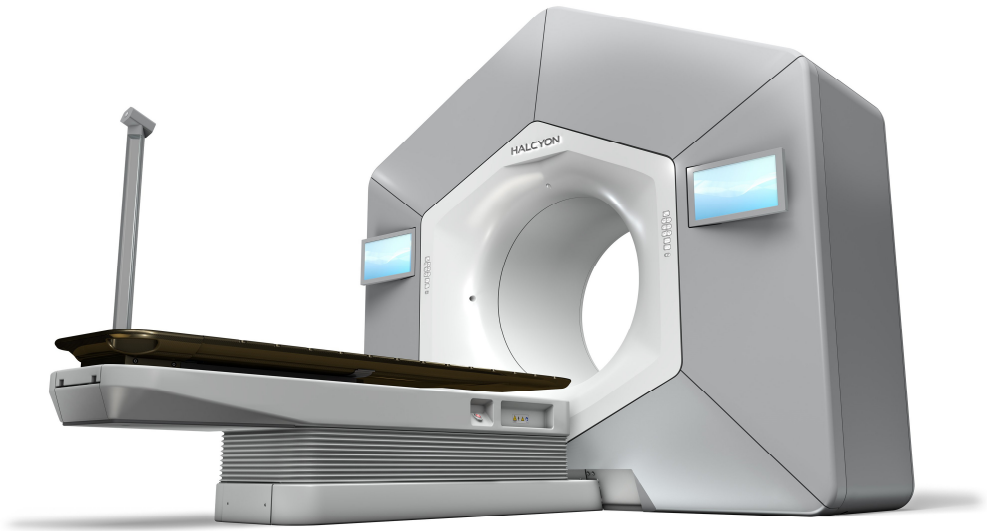
From 2D to 3D: cobalt





From 2D to 3D: linac





Learned clinical needs #4

Improved 3D dose distribution leads to less toxicity and higher tumor control

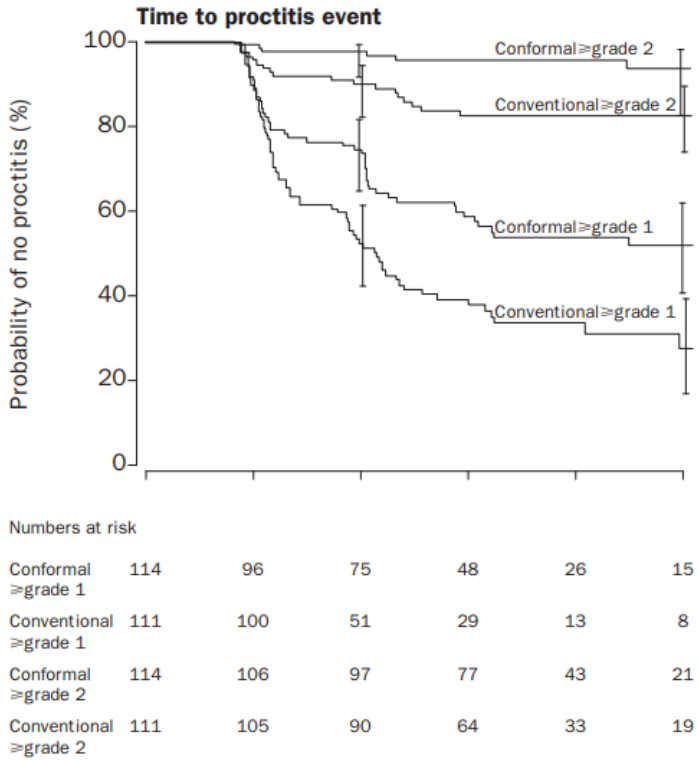
From 2D to 3D: normal tissue toxicity

Clinical Trial > Lancet. 1999 Jan 23;353(9149):267-72. doi: 10.1016/S0140-6736(98)05180-0.

Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial

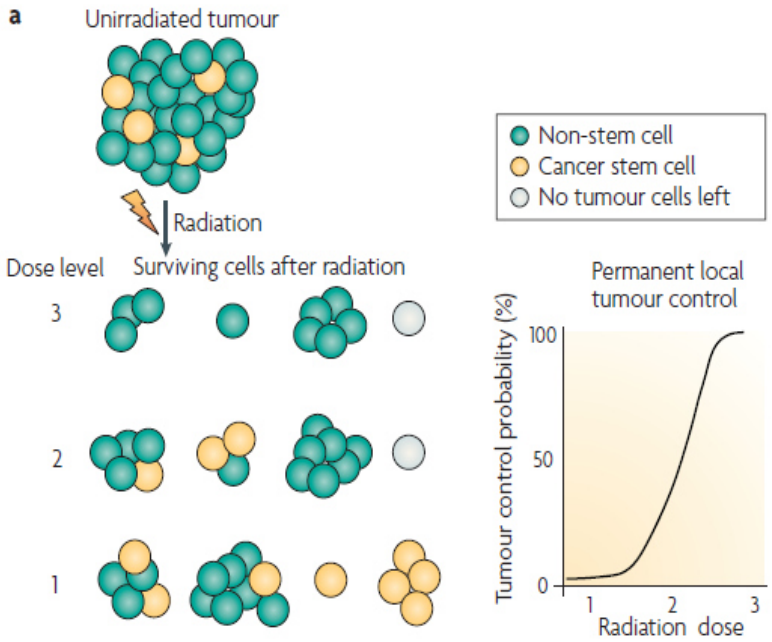
D P Dearnaley [1], V S Khoo, A R Norman, L Meyer, A Nahum, D Tait, J Yarnold, A Horwich

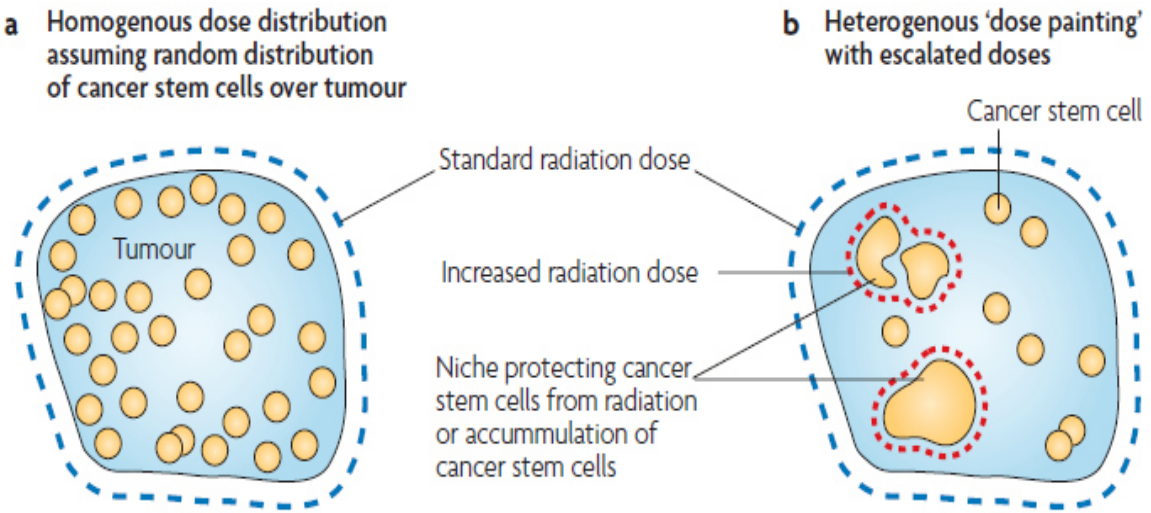
From 2D to 3D: normal tissue toxicity



Significantly fewer men developed radiation-induced proctitis (37% vs 56% ≥RTOG grade 1, p=0.004) and bleeding (5% vs 15% ≥RTOG grade 2, p=0.01) in the conformal group than in the conventional group

From 2D to 3D: tumor control probability



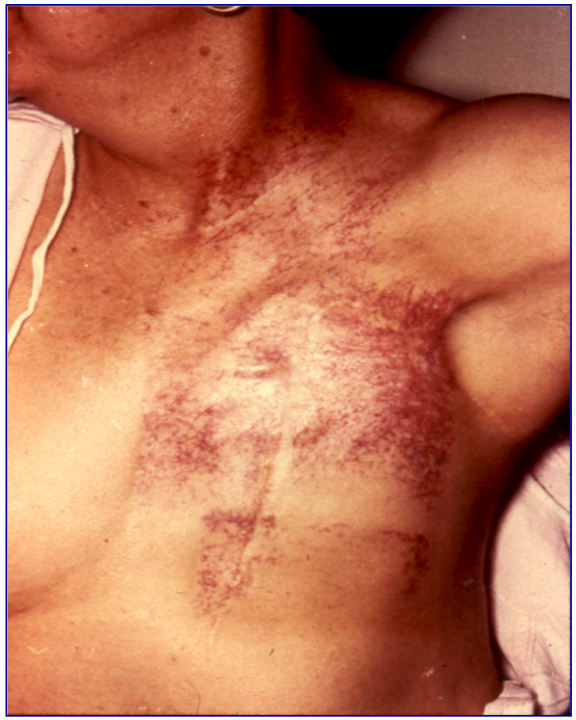


Learned clinical needs #5

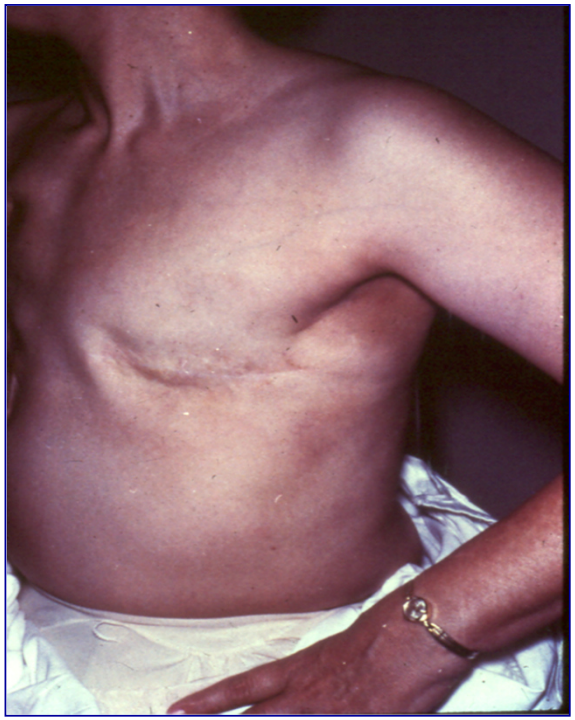
Moving away from 2 Gy …

Moving away from 2~~D~~ Gy…

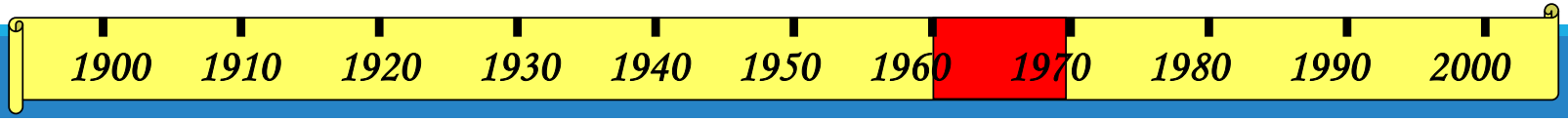
Fraction ***size*** is important for ***late damage***



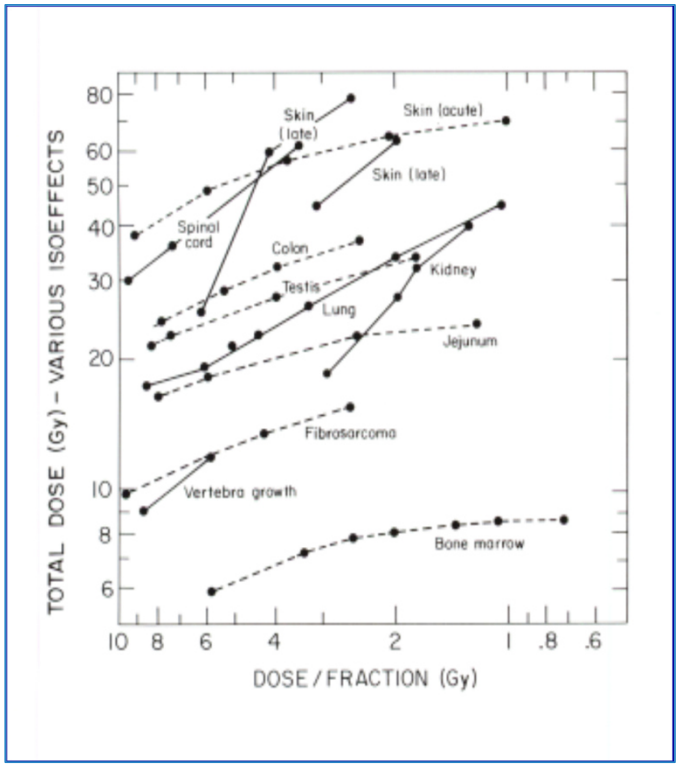
3 x 3.3 Gy



5 x 2 Gy



Moving away from 2~~0~~ Gy…



Rome and the spaghetti plot

NEOPLASMS

02NLM: QZ 269 I623 1981p Cit. No. 8305714

Rome International Symposium (2nd : 1980). Biological bases and clinical implications of tumor radioresistance / editors, Gilbert H. Fletcher, Carlo Nervi, H. Rodney Withers ; associate editors, Giorgio Arcangeli, Francesco Mauro, Norah duV. Tapley. -- New York : Masson Pub. USA, c1983. -- xv, 429 p. : ill. "Proceedings of the 2nd Rome International Symposium, September 21-24, 1980, Rome, Italy."--T.p. verso.
02NLM: W3 RO683D 2nd 1980b
0XNLM: [QZ 269 R763 1980b]
Cit. No. 8211809 (rev. CIP.)

Moving away from 2~~0~~ Gy…

The spectrum theory: Hellmann & Weichselbaum

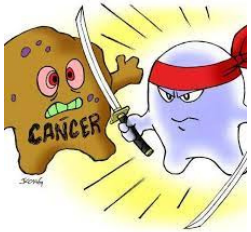
Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

Hellman & Weichselbaum, JCO 1995

Moving away from 2~~D~~ Gy…

Stereotactic Body RadioTherapy



Working mechanism

- Different as compared to conventional fractionation

Conventional fractionation	SBRT
Local effect	Local & systemic (abscopal) effect
Through (in)direct tumor cell death (DNA damage)	Endothelial apoptosis Reprogramming of the tumor micro-environment

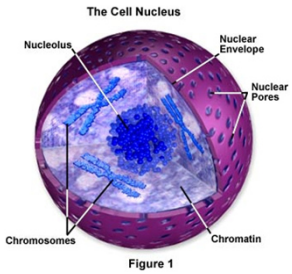
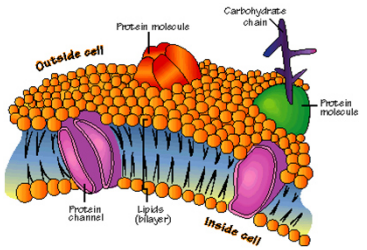


Figure 1



Moving away from 2D Gy…

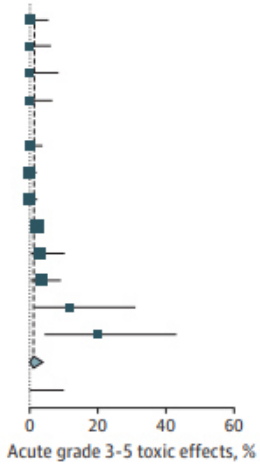
Safety and survival rates associated with ablative SBRT for patients with oligometastatic cancer: a systematic review and meta-analysis

Figure 2. Safety

A Acute grade 3-5 toxic effects

Source	Cases, n	Total patients, n	Median age, y	Median dose	Acute grade 3-5 toxic effects, % (95% CI)
Ahmed et al,[13] 2013 (prostate)	0	17	65.0	20 Gy/1 fx; 8-24 Gy/1-3 fx	0.0 (0.0-5.5)
Chang et al,[14] 2004 (mixed)	0	15	50.0	30-37.5 Gy/3 fx	0.0 (0.0-6.3)
Henke et al,[16] 2018 (mixed)	0	11	64.0	50 Gy/5 fx	0.0 (0.0-8.5)
Iyengar et al,[18] 2018 (NSCLC)	0	14	63.5	16-24 Gy/1 fx; 26.5-33 Gy/3 fx; 30-37.5 Gy/5 fx	0.0 (0.0-6.7)
Ost et al,[23] 2018 (prostate)	0	25	70.0	30 Gy/3 fx	0.0 (0.0-3.8)
Rusthoven et al,[27] 2009 (mixed)	0	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	0.0 (0.0-2.0)
Scorsetti et al,[29] 2015 (mixed)	0	42	67.0	75 Gy/3 fx	0.0 (0.0-2.3)
Sutera et al,[31] 2019 (mixed)	3	147	66.4	48 Gy/4 fx	2.0 (0.4-4.9)
Rusthoven et al,[26] 2009 (mixed)	1	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	2.6 (0.0-10.0)
Salama et al,[28] 2012 (mixed)	2	61	64.4	20-60 Gy/3 fx	3.3 (0.3-9.2)
Méndez Romero et al,[19] 2006 (mixed)	2	17	63.0	30-37.5 Gy/3 fx	11.8 (1.3-31.1)
David et al,[33] 2020 (breast)	3	15	63.0	20 Gy/1 fx; 28 Gy/2 fx	20.0 (4.4-43.1)
Random-effects model		449			1.2 (0.0-3.8)
Prediction interval					(0.0-10.1)

Heterogeneity: I^2 = 50% (95% CI, 3%-74%), τ = 0.20% (95% CI, 0.00-1.43), χ^2_{11} = 22.09 (P = .02)



Moving away from 2D Gy…

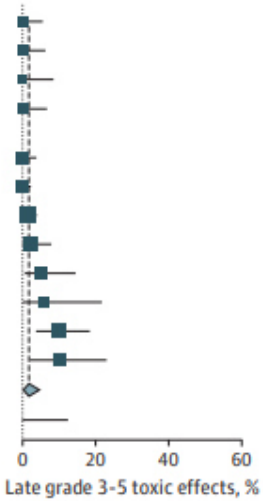
Safety and survival rates associated with ablative SBRT for patients with oligometastatic cancer: a systematic review and meta-analysis

Figure 2. Safety

B Late grade 3-5 toxic effects

Source	Cases, n	Total patients, n	Median age, y	Median dose	Late grade 3-5 toxic effects, % (95% CI)
Ahmed et al,[13] 2013 (prostate)	0	17	65.0	20 Gy/1 fx; 8-24 Gy/1-3 fx	0.0 (0.0-5.5)
Chang et al,[14] 2004 (mixed)	0	15	50.0	30-37.5 Gy/3 fx	0.0 (0.0-6.3)
Henke et al,[16] 2018 (mixed)	0	11	64.0	50 Gy/5 fx	0.0 (0.0-8.5)
Iyengar et al,[18] 2018 (NSCLC)	0	14	63.5	16-24 Gy/1 fx; 26.5-33 Gy/3 fx; 30-37.5 Gy/5 fx	0.0 (0.0-6.7)
Ost et al,[23] 2018 (prostate)	0	25	70.0	30 Gy/3 fx	0.0 (0.0-3.8)
Scorsetti et al,[29] 2015 (mixed)	0	42	67.0	75 Gy/3 fx	0.0 (0.0-2.3)
Sutera et al,[31] 2019 (mixed)	2	147	66.4	48 Gy/4 fx	1.4 (0.1-3.9)
Rusthoven et al,[27] 2009 (mixed)	1	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	2.1 (0.0-7.9)
Rusthoven et al,[26] 2009 (mixed)	2	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	5.3 (0.5-14.5)
Méndez Romero et al,[19] 2006 (mixed)	1	17	63.0	30-37.5 Gy/3 fx	5.9 (0.0-21.7)
Salama et al,[28] 2012 (mixed)	6	61	64.4	20 Gy/1 fx; 28 Gy/2 fx	9.8 (3.7-18.4)
Nuyttens et al,[22] 2015 (mixed)	3	30	66.0	60 Gy/3 fx; 30 Gy/1 fx	10.0 (2.0-23.0)
Random-effects model		464			1.7 (0.2-4.6)
Prediction interval					(0.0-12.5)

Heterogeneity: I^2 = 54% (95% CI, 11%-76%), τ = 0.25% (95% CI, 0.01%-1.00%), χ^2_{11} = 23.79 (P = .01)



Moving away from 2D Gy…

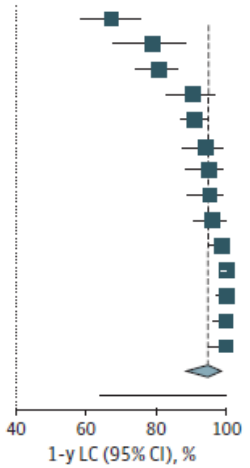
Safety and survival rates associated with ablative SBRT for patients with oligometastatic cancer: a systematic review and meta-analysis

Figure 3. Clinical Benefit

A 1-y Local control

Source	Cases, n	Total patients, n	Median age, y	Median dose	1-y LC (95% CI), %
Salama et al,[28] 2012 (mixed)	76	113	64.4	20-60 Gy/3 fx	67.3 (58.3-75.5)
Nuyttens et al,[22] 2015 (mixed)	45	57	66.0	60 Gy/3 fx; 30 Gy/1 fx	78.9 (67.6-88.5)
Wang et al,[32] 2012 (mixed)	134	166	58.0	27-30 Gy/3 fx	80.7 (74.1-86.2)
Garg et al,[15] 2012 (mixed)	57	63	61.0	16-24 Gy/1 fx	90.5 (82.8-96.8)
Sutera et al,[31] 2019 (mixed)	198	218	66.4	48 Gy/4 fx	90.8 (86.9-94.4)
Scorsetti et al,[29] 2015 (mixed)	49	52	67.0	75 Gy/3 fx	94.2 (87.5-99.2)
Rusthoven et al,[27] 2009 (mixed)	60	63	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	95.2 (88.3-99.0)
Muacevic et al,[21] 2013 (prostate)	61	64	66.0	20.2 Gy/1 fx	95.3 (89.1-99.2)
Siva et al,[30] 2018 (prostate)	48	50	70.0	20 Gy/1 fx	96.0 (90.5-99.9)
Pasqualetti et al,[25] 2018 (prostate)	77	78	NR	24 Gy/1 fx; 27 Gy/3 fx	98.7 (95.0-100)
Rusthoven et al,[26] 2009 (mixed)	63	63	58.0	Ph I: 48–60 Gy/3 fx; Ph 2: 60 Gy/3 fx	100 (98.5-100)
Méndez Romero et al,[19] 2006 (mixed)	34	34	63.0	30-37.5 Gy/3 fx	100 (97.2-100)
Ost et al,[23] 2018 (prostate)	25	25	70.0	30 Gy/3 fx	100 (96.2-100)
David et al,[33] 2020 (breast)	19	19	63.0	20 Gy/1 fx	100 (95.0-100)
Random-effects model		1065			94.7 (88.6-98.6)
Prediction interval					(63.8-100)

Heterogeneity: I^2 = 90% (95% CI, 86%-94%), τ = 0.81% (95% CI, 0.36%-2.38%), χ^2_{13} = 135.99 (*P* <.01)



Moving away from 2~~D~~ Gy…

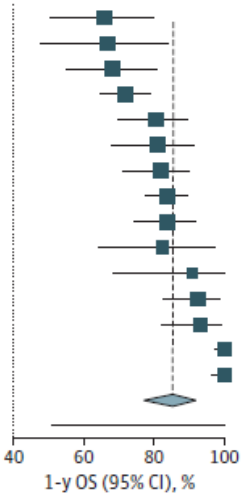
Safety and survival rates associated with ablative SBRT for patients with oligometastatic cancer: a systematic review and meta-analysis

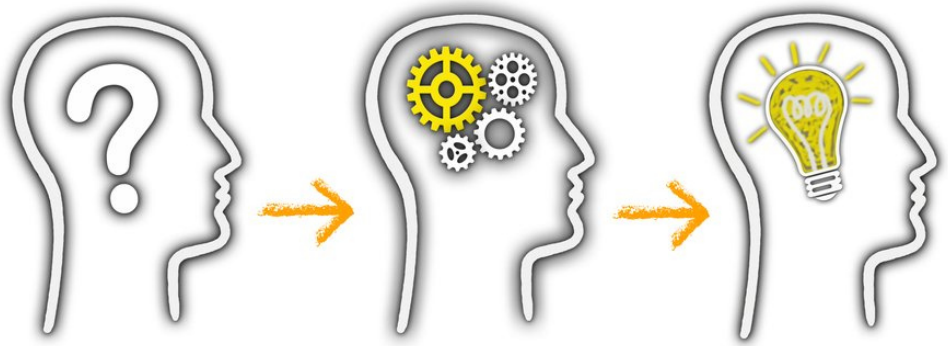
Figure 3. Clinical Benefit

B 1-y Overall survival

Source	Cases, n	Total patients, n	Median age, y	Median dose	1-y OS (95% CI), %
Rusthoven et al,[26] 2009 (mixed)	25	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	65.8 (50.3-79.9)
Iyengar et al,[17] 2014 (NSCLC)	16	24	67.0	19-24 Gy/1fx; 27-33 Gy/3 fx; 35-40 Gy/5 fx	66.7 (47.6-84.1)
Rusthoven et al,[27] 2009 (mixed)	32	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	68.1 (54.8-80.9)
Wang et al,[32] 2012 (mixed)	107	149	58.0	27-30 Gy/3 fx	71.8 (64.4-78.8)
Garg et al,[15] 2012 (mixed)	49	61	61.0	16-24 Gy/1 fx	80.3 (69.6-89.3)
Scorsetti et al,[29] 2015 (mixed)	34	42	67.0	75 Gy/3 fx	81.0 (68.0-91.3)
Salama et al,[28] 2012 (mixed)	50	61	64.4	20-60 Gy/3 fx	82.0 (70.9-90.2)
Sutera et al,[31] 2019 (mixed)	123	147	66.4	48 Gy/4 fx	83.7 (77.7-89.5)
Palma et al,[24] 2019 (mixed)	56	66	67.0	36-60 Gy/3-8 fx; 16-24 Gy/1fx	83.6 (74.5-91.8)
Méndez Romero et al,[19] 2006 (mixed)	14	17	63.0	30-37.5 Gy/3 fx	82.4 (64.0-97.2)
Henke et al,[16] 2018 (mixed)	10	11	64.0	50 Gy/5 fx	90.9 (68.1-100)
Milano et al,[20] 2009 (breast)	37	40	48.0	NR	92.5 (82.7-98.6)
Nuyttens et al,[22] 2015 (mixed)	28	30	66.0	60 Gy/3 fx; 30 Gy/1 fx	93.3 (82.3-99.4)
Siva et al,[30] 2018 (prostate)	33	33	70.0	20 Gy/1 fx	100 (97.1-100)
Ost et al,[23] 2018 (prostate)	25s	25	70.0	30 Gy/3 fx	100 (96.2-100)
Random-effects model		791			85.3 (77.0-92.0)
Prediction interval					(50.8-100)

Heterogeneity: I^2 = 82% (95% CI, 71%-88%), τ = 0.72% (95% CI, 0.30%-2.09%), χ^2_{14} = 75.85 (P <.01)





Learned clinical needs #6

A radiation oncologist is 4D superior to 3D!

A real radiation oncologist …

The stethoscope

The laryngoscope

The digital probe

Learned clinical needs

Conclusions

Conclusion (1)

Lessons learned

#1 We need accurate 3D image information to define and delineate the target and to avoid the OAR

#2 We need powerful dose calculation algorithms to accurately determine the dose to be delivered

#3 We need the right radiation technology to deliver the correct 3D dose distribution

#4 Improved 3D dose distribution leads to less toxicity and higher tumor control

#5 Moving away from 2 Gy …

#6 A radiation oncologist is 4D superior to 3D!

Conclusion (2)

The greatest challenge for radiation therapy,

i.e. **to obtain the highest probability of cure with the least morbidity**,

still remains!

But going from 2D to 3D

brought us already an important step closer to that goal!