Pancreatic Cancer UK

Virtual National Study Sessions

October 2020

Treatment | Dietetic Management | Emotional Support

#PCUKStudyDay

SABR: The Latest Development in Radiotherapy

Monday 5th October 2020, 13.00 – 14.00

The opportunities of Stereotactic Ablative Body Radiotherapy (SABR) for locally advanced unresectable pancreatic cancer

An overview

Outline of session

- Principles and practice of Stereotactic Ablative Body Radiotherapy (SABR)
  - specific utility and challenges in Pancreatic cancer
- Evidence base for SABR in Pancreatic Cancer
  - Published data, Patient – public input and UK Clinical Oncology perspectives
- Future developments on the horizon
  - Promise of newer technologies

Core principles for Precision RT

- Image Guided RT = IGRT
  - Patient derived treatment volumes (personalised)
  - Adaptive Treatment (on line imaging)
  - Motion management
- High Dose to Target Volume
  - Increasing Biological effective doses (BED)
    - dose per treatment higher than conventional regimes (e.g. SABR)
    - Addition of drug
- Maximal sparing of normal tissue
  - Dose sculpting
  - Knowing when / how to compromise dose / target coverage

SABR

– Stereotactic ablative body radiotherapy (SABR) refers to the precise irradiation of an image-defined extra-cranial lesion with the use of high radiation dose in a small number of fractions

UK SABR Consortium guidelines 2013

Linear Accelerators

Principles of radiation therapy in Pancreatic tumours

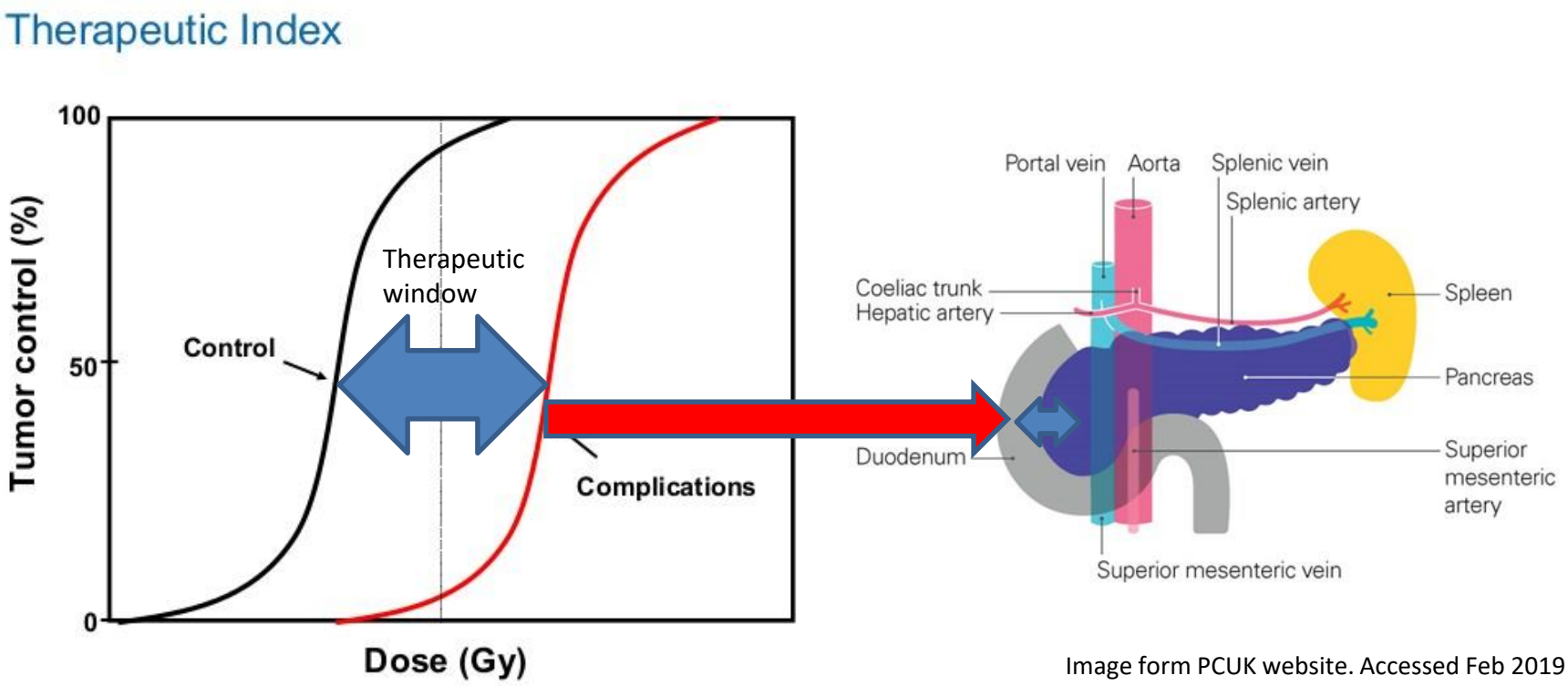
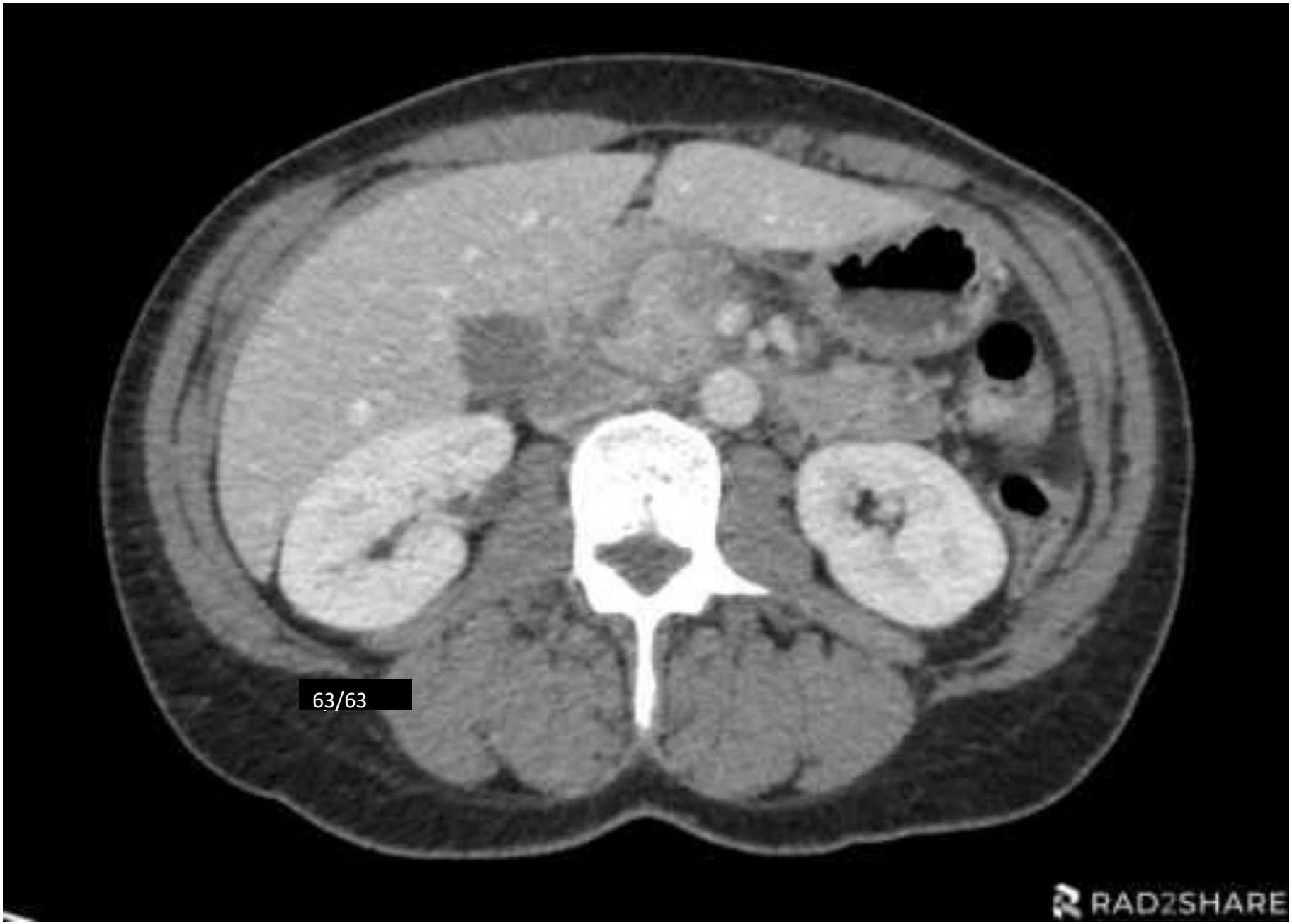


Image form PCUK website. Accessed Feb 2019

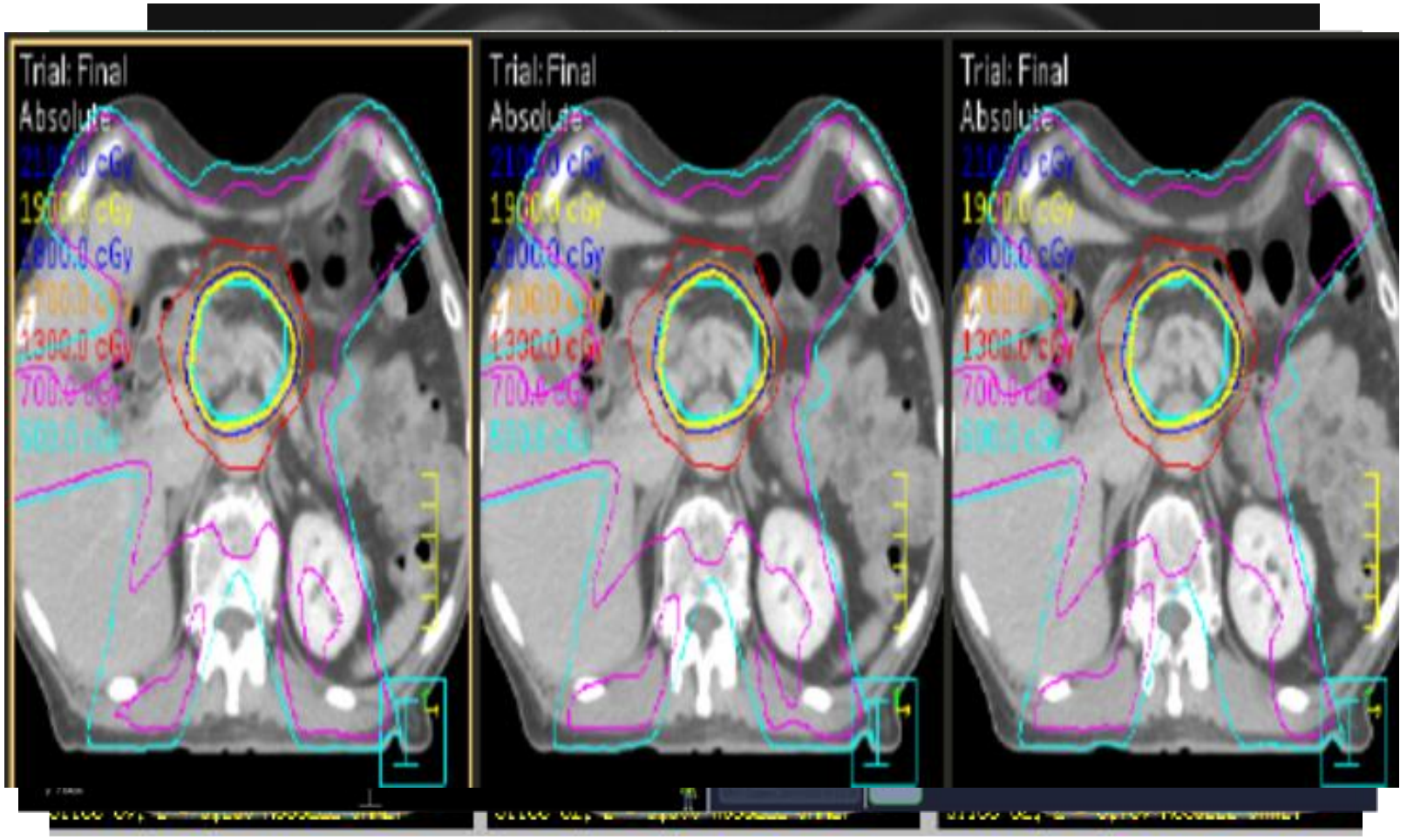
Pancreatic RT challenges

- Target Volume delineation
  - Difficult to outline
  - Imaging underestimates tumour
- Organs at Risk
  - Close proximity
  - Narrow therapeutic index
- Motion

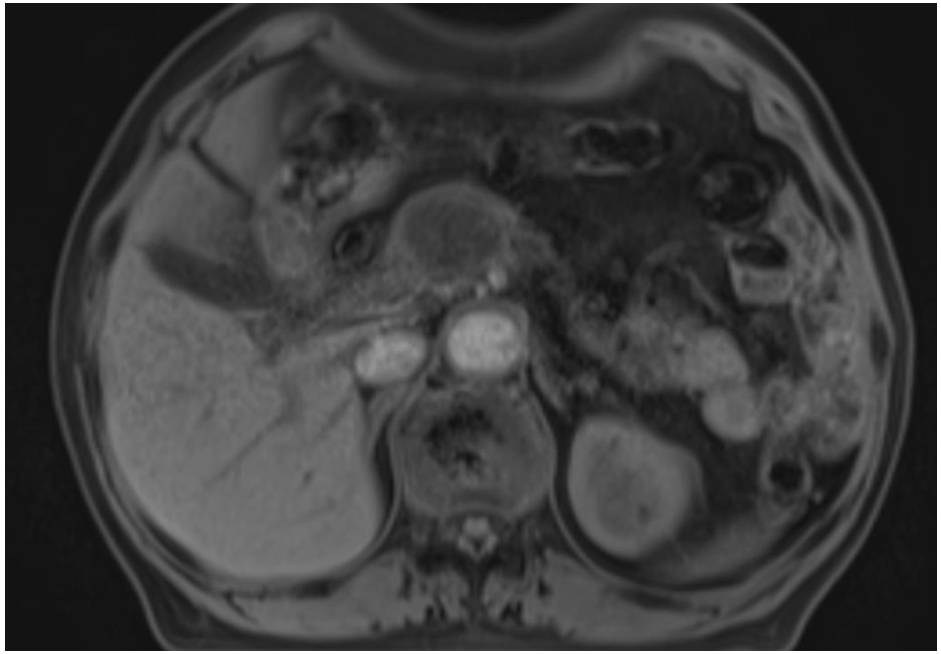

63/63
RAD2SHARE

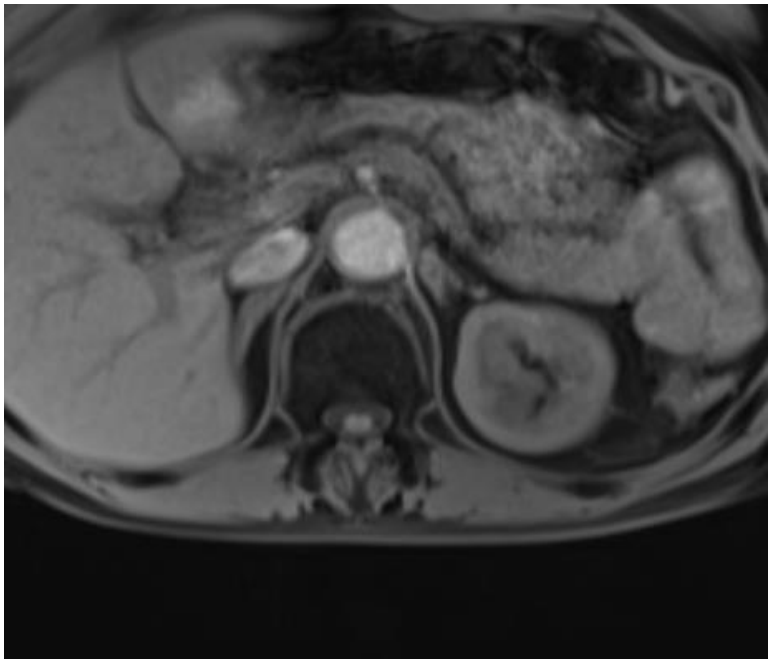

26/26
RAD2SHARE

Case study – current practice



Personalised Adaptive RT case





Radiotherapy and Oncology 121 (2016) 86–91

Contents lists available at ScienceDirect

Radiotherapy and Oncology

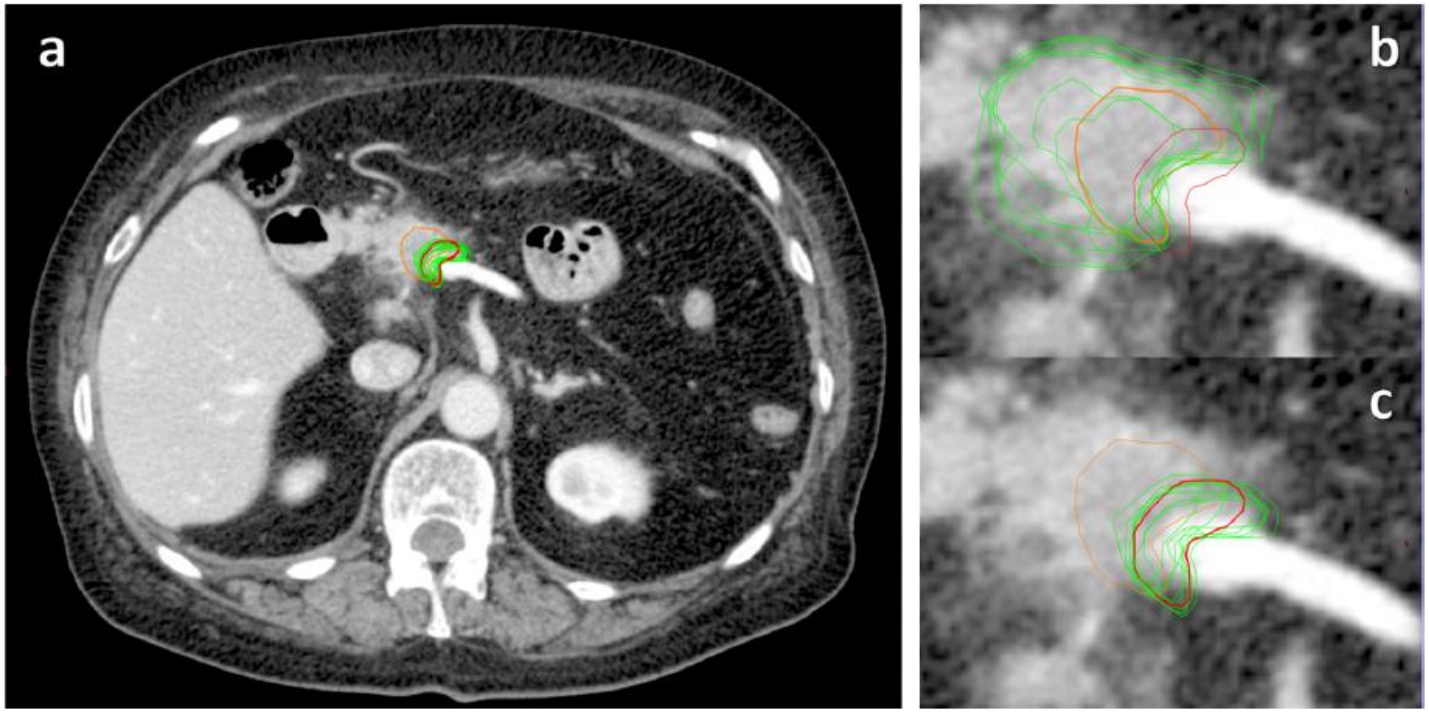
journal homepage: www.thegreenjournal.com

Pancreatic cancer SBRT

Conformity analysis to demonstrate reproducibility of target volumes for Margin-Intense Stereotactic Radiotherapy for borderline-resectable pancreatic cancer

Daniel L.P. Holyoake [a,e], Maxwell Robinson [a,e], Derek Grose [b], David McIntosh [b], David Sebag-Montefiore [c,d], Ganesh Radhakrishna [d], Neel Patel [e], Mike Partridge [a], Somnath Mukherjee [a,e], Maria A. Hawkins [a,e,*]

[a] CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford; [b] The Beatson West of Scotland Cancer Centre, Glasgow; [c] University of Leeds, CRUK Leeds Centre; [d] Leeds Cancer Centre, St James's University Hospital, Leeds; and [e] The Churchill Hospital, Oxford, UK



Radiotherapy and Oncology 120 (2016) 212–216

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Target volume definition

Comparison of investigator-delineated gross tumour volumes and quality assurance in pancreatic cancer: Analysis of the on-trial cases for the SCALOP trial

Emmanouil Fokas[a,1], Emiliano Spezi[b,1], Neel Patel[c], Chris Hurt[d], Lisette Nixon[d], Kwun-Ye Chu[a,c], John Staffurth[e,f], Ross Abrams[g], Somnath Mukherjee[a,c,*]

[a]Department of Oncology, CRUK/MRC Institute for Radiation Oncology, University of Oxford; [b]School of Engineering, Cardiff University; [c]Oxford University Hospital NHS Foundation Trust; [d]Wales Cancer Trials Unit, Centre for Trials Research; [e]Institute of Cancer and Genetics, Cardiff University; [f]Cardiff NCRI RTTQA Centre, Velindre NHS Trust, UK; [g]Department of Radiation Oncology, Rush University Medical Center, Chicago, USA

		Univariable analysis				Multivariable analysis			
		n	Odds ratio	95% CIs	*p*	*n*	Odds ratio	95% CIs	*p*
gsGTV	continuous	58	1.02	0.98–1.05	0.341	58	0.99	0.96–1.04	0.876
JCI GTV	<0.7	32	1.00			32	1.00		
	⩾0.7	26	5.71	1.81–18.08	0.003	26	7.43	1.86–29.7	0.005
JCI PTV	<0.8	28	1.00						
	⩾0.8	30	2.5	0.84–7.42	0.099				
Trial arm	Gem	35	1.00			27	1.00		
	Cape	35	0.63	0.24–1.62	0.335	31	0.57	0.15-2.21	0.417
WHO PS	0	29	1.00			24	1.00		
	1–2	41	1.41	0.54–3.73	0.484	34	1.45	0.39–5.43	0.583
Sex	Male	40	1.00			34	1.00		
	Female	30	2.12	0.81–5.59	0.127	24	2.94	0.77–11.21	0.113
Age	<65	36	1.00			30	1.00		
	⩾65	34	0.55	0.21–1.42	0.216	28	1.43	0.33–6.11	0.632
RT fractions	0–26	12	1.00			10	1.00		
	27+	50	0.47	0.13–1.66	0.240	48	0.57	0.11–3.03	0.508

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Pancreatic cancer

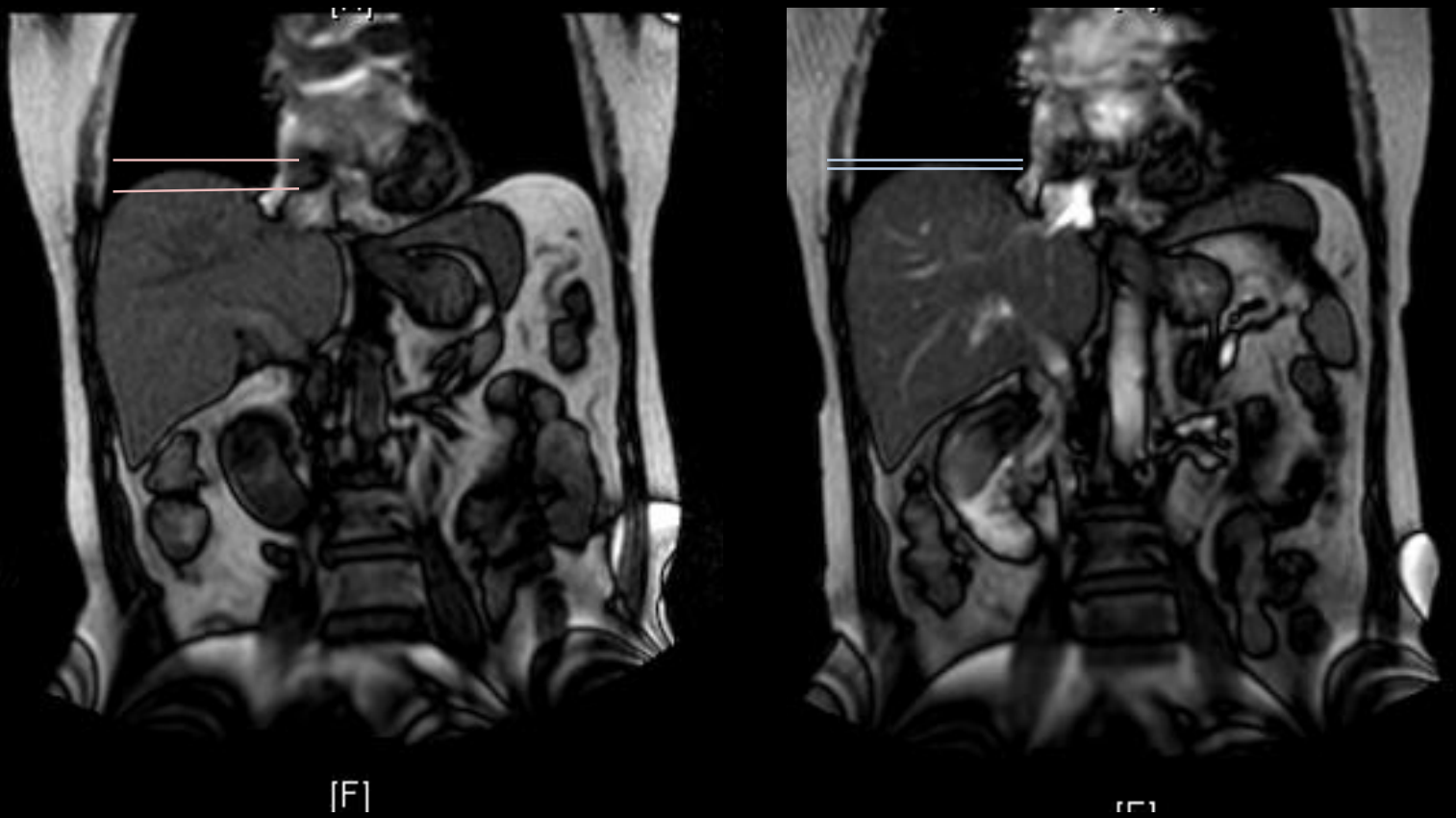
MRI-based tumor motion characterization and gating schemes for radiation therapy of pancreatic cancer

Hanne D. Heerkens [a,*], Marco van Vulpen [a], Cornelis A.T. van den Berg [a], Rob H.N. Tijssen [a], Sjoerd P.M. Crijns [a], Izaak Q. Molenaar [b], Hjalmar C. van Santvoort [b], Onne Reerink [a], Gert J. Meijer [a]

[a] Department of Radiotherapy; and [b] Department of Surgery, University Medical Center Utrecht, The Netherlands

Motion management strategies crucial for precision RT delivery


27/27
RAD2SHARE



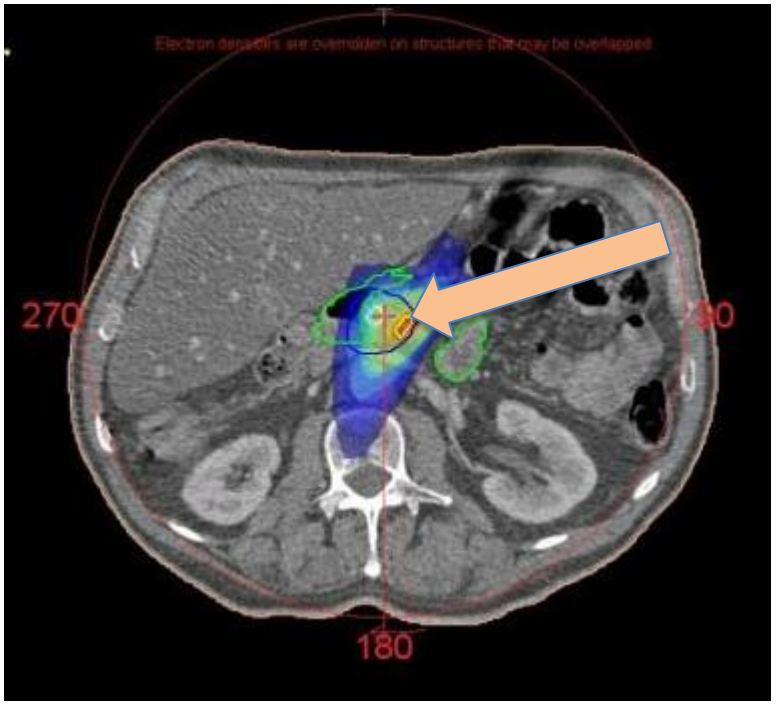
Slide courtesy John Rogers & Lisa McDaid

The evidence build

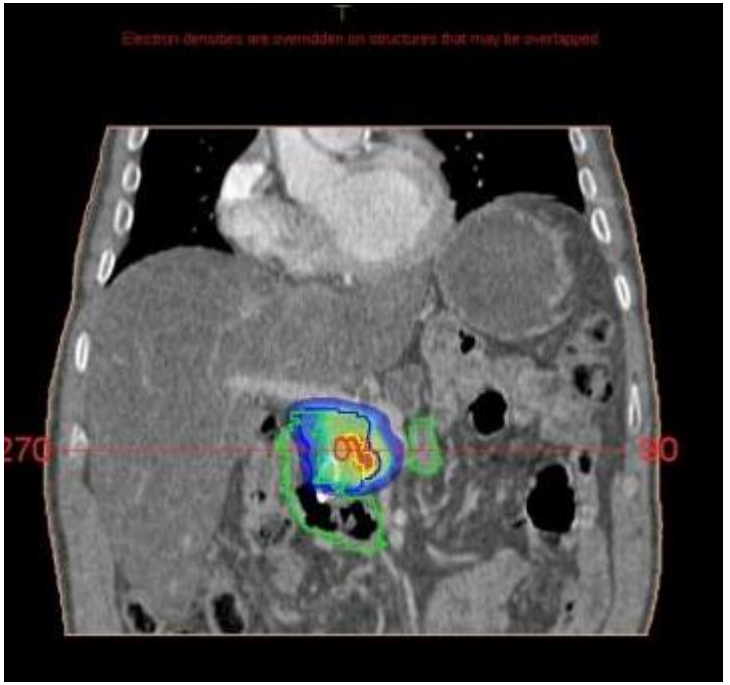
SABR FOR PANCREATIC CANCER

Margin Intensive SABR

- High dose to vessel contact



- Dose sculpting away from duodenum



SPARC trial – multicentre UK trial (CI = Maria Hawkins)

Pooled analysis SABR for LAPC

- 19 published series (1009 pts); follow up 6-21 months
- Heterogeneous with including LAPC and BRPC, different SACT schedules and regimens, variable dose- fractionation, varying platforms

- BED_{10} 37.5 – 120 Gy
- 1 year OS = 51.6% (13 trials) median OS = 5.7 – 47 months

- Local Control rates = 72.3% (95%CI 58.5%- 79%)
  - Total dose and higher fractions significantly better 1year LCR

- PFS = 4.8 – 27 months

- Toxicity = late G3/4 < 11% ;
  - in 6 series g3/4 rate 0%

Petrelli et al. IJROBP 2017: 97(2)

Level 1B evidence

Cancer

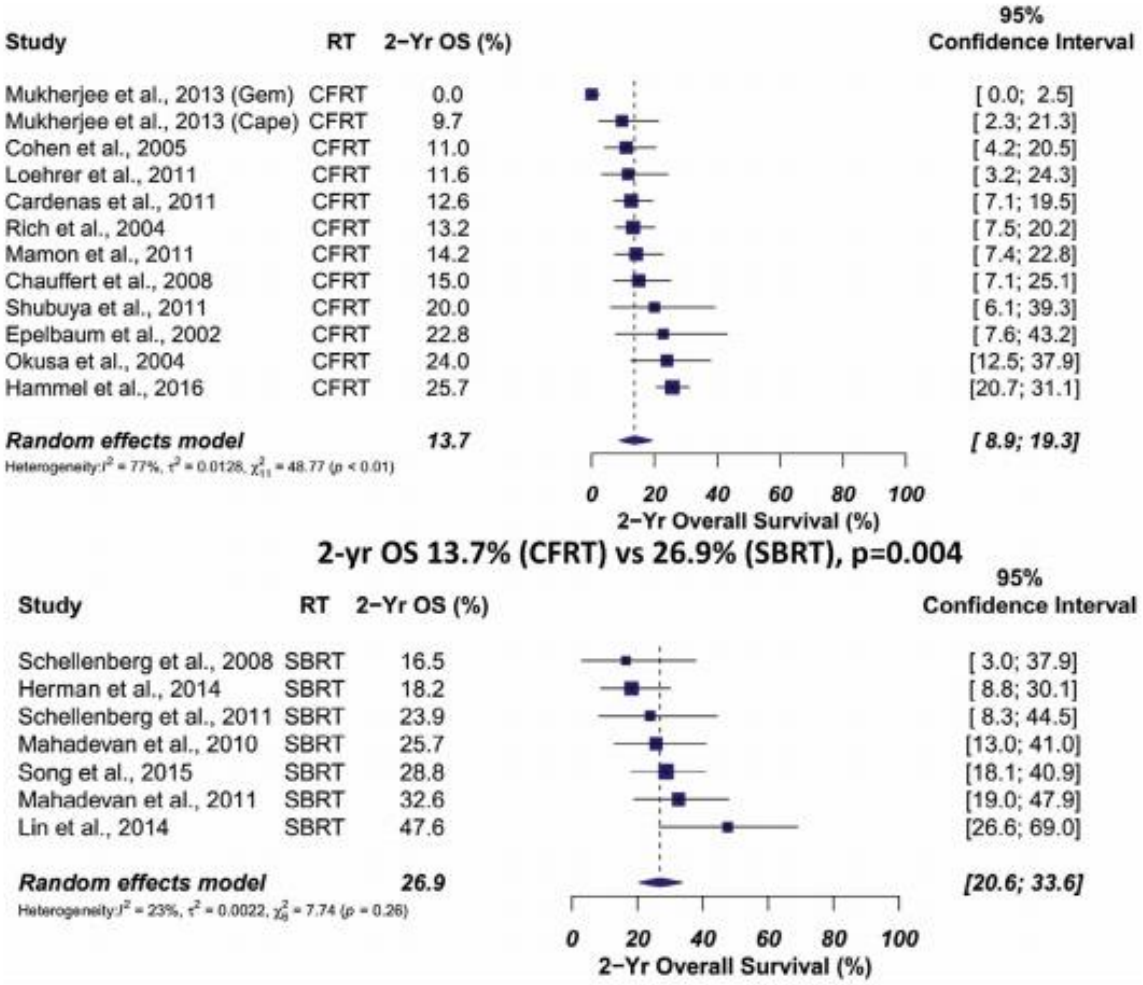
Original Article

Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRiSP): An international systematic review and meta-analysis

Leila T. Tchelebi MD ✉, Eric J. Lehrer MD, Daniel M. Trifiletti MD, Navesh K. Sharma DO, Niraj J. Gusani MD, MS, Christopher H. Crane MD, Nicholas G. Zaorsky MD

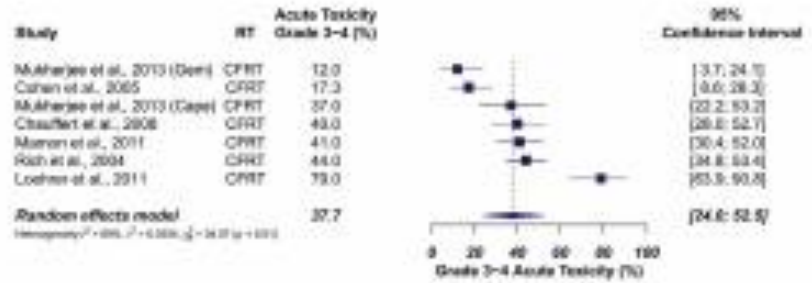
First published: 03 March 2020 | https://doi.org/10.1002/cncr.32756 | Citations: 5

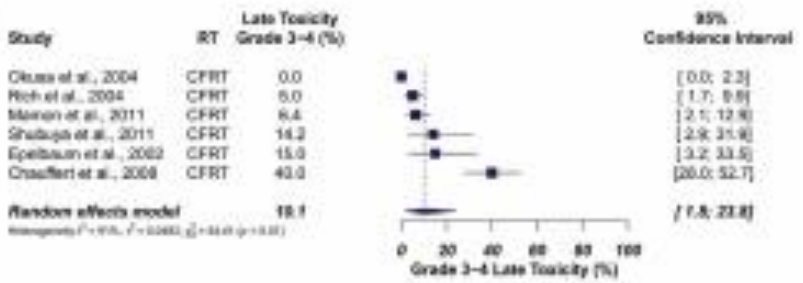
2 year survival



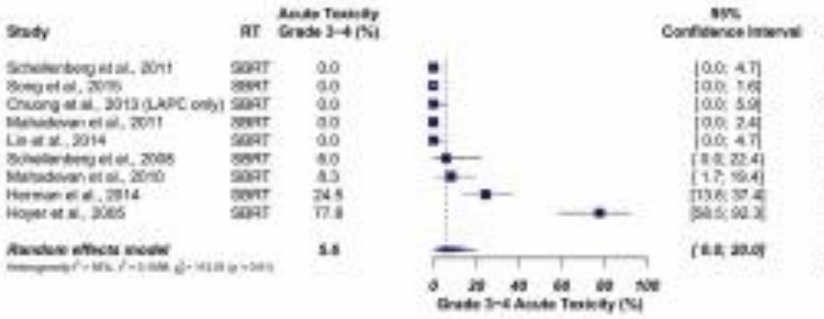
Superior 2Yr OS favouring SABR (statistically significant p< 0.05)

Side effect profile

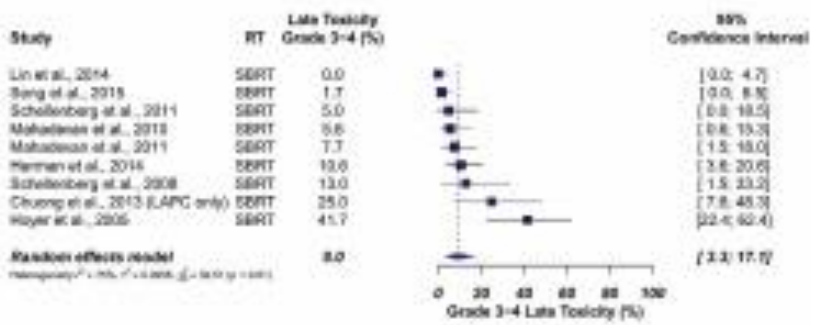




Grade 3-4 Acute Tox 37.7% (CFRT) vs 5.6 % (SBRT), p=0.013



Grade 3-4 Late Tox 10.1% (CFRT) vs 9.0 % (SBRT), p=0.85



Potential benefits of SABR

- Reduction in number of treatment visits
  - Jones, C.M., *et al. Br J Cancer* **123,** 709–713 (2020).
- Longer freedom from treatment time / PFS
  - Suker et al. EClinialMed 17(2019)
- Improved local control
  - Tangible benefit in reduction in pain
    - Herman et al. Cancer April 2015
- Effects of SABR beyond primary disease control
  - Griffin et al. IJROBP 2020. 107(4); 766-778
- Improved tolerability

Patient- carer perspective

- The PPE was conducted in a virtual format
  - online survey (8 participants) or join an online focus group with Consultant Clinical Oncologists (5 participants).
    - Baseline knowledge was low with 50% having no prior knowledge of SABR and 75% unaware of its role in LAPC.
  - If SABR was offered 92.3% (12 of 13) would opt for this as the treatment of choice over CRT
    - discussions highlighted that the rationale for this approach should be clearly presented.
    - Experience and expertise in technique
  - The group emphasised quality of life as a key potential advantage of SABR,
    - 100% feeling avoidance of chemotherapy, and 87.5% reduction in hospital visits -important or very important.
  - 75% were prepared to travel for access to SABR.

Clinical Oncologists perspective

- 25 HPB Clinical Oncology consultants across 21 UK centres.
- Support for SABR in LAPC was high:
- 100% felt it would be supported by local MDT
  - 96% agreed to offer within this indication.
- Capacity for implementation was limited with only 68% of centres able to adapt current equipment for abdominal SABR
- 72% requiring support to establish the service in their centre.
- Suggestions included external peer review (73% support), CPD accredited training (68% support) and mentoring from another institution (43% support).

The promise of newer technology

IMPROVING THE THERAPEUTIC INDEX

MR_Linac

Practical Radiation Oncology (2017) 7, 126–136

www.practicalradonc.org

Original Report

Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer

H.D. Heerkens MD [a], W.A. Hall MD [b], X.A. Li PhD [b], P. Knechtges MD [c], E. Dalah PhD [b,d], E.S. Paulson PhD [b], C.A.T. van den Berg PhD [a], G.J. Meijer PhD [a], E.J. Koay MD, PhD [e], C.H. Crane MD [e], K. Aitken MD [f], M. van Vulpen MD, PhD [a], B.A. Erickson MD [b,*]

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[b]*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[c]*Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[d]*Medical Diagnostic Imaging Department, College of Health and Science, University of Sharjah, Sharjah, Dubai*
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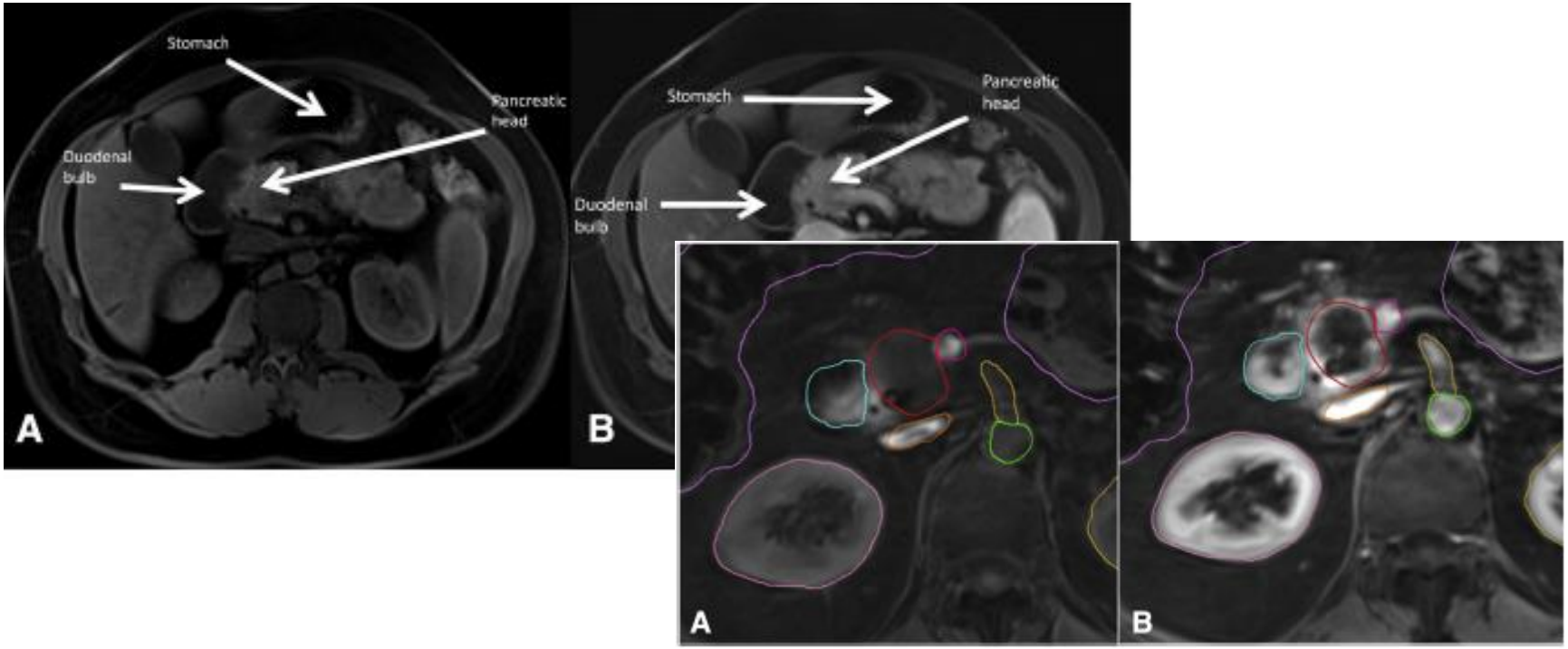
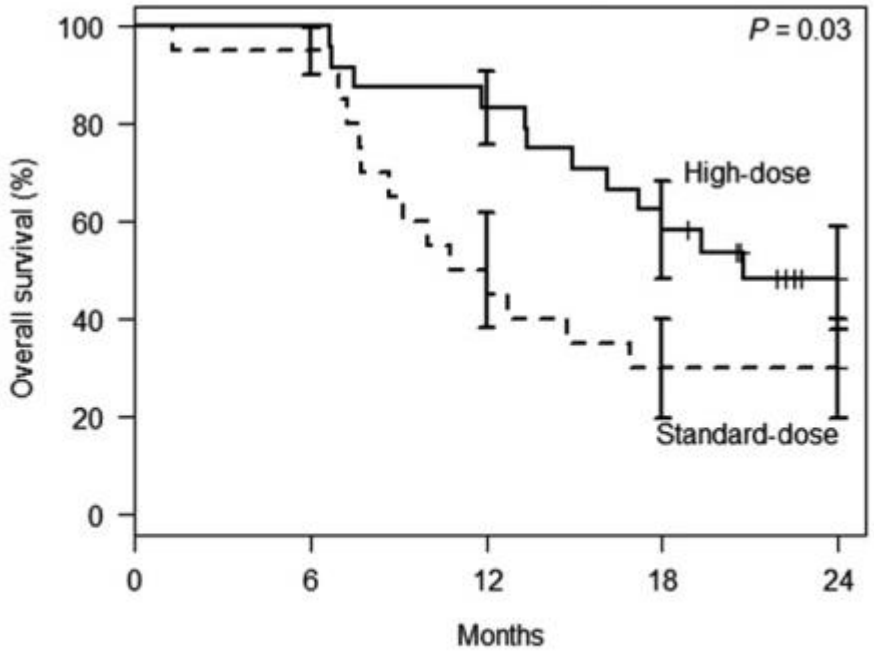
Received 8 September 2016; accepted 10 October 2016



Dose escalation with MRgRT



High-dose	24	24	20	14	5
Standard-dose	20	19	10	6	5

Multicentre, retrospective cohort form 5 centres

Improved outcomes with BED > 70Gy

- 2 year OS high dose vs. standard dose = 49% vs. 30 %
- 2 year FFLP high dose vs. standard dose = 77% vs. 57%

Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. Cancer Med. 2019;8(5):2123-2132.

Stereotactic MR guided Adaptive Radiotherapy
SMART

- Development of Phase 2 studies underway

- Opportunity to evaluate dose escalation with MRgRT

AM Bruynzeel & FJ Lagerwaard. Clin Transl Radiat Oncol 2019; 18: 128-130

The Equipment: Varian Probeam

Example planning study

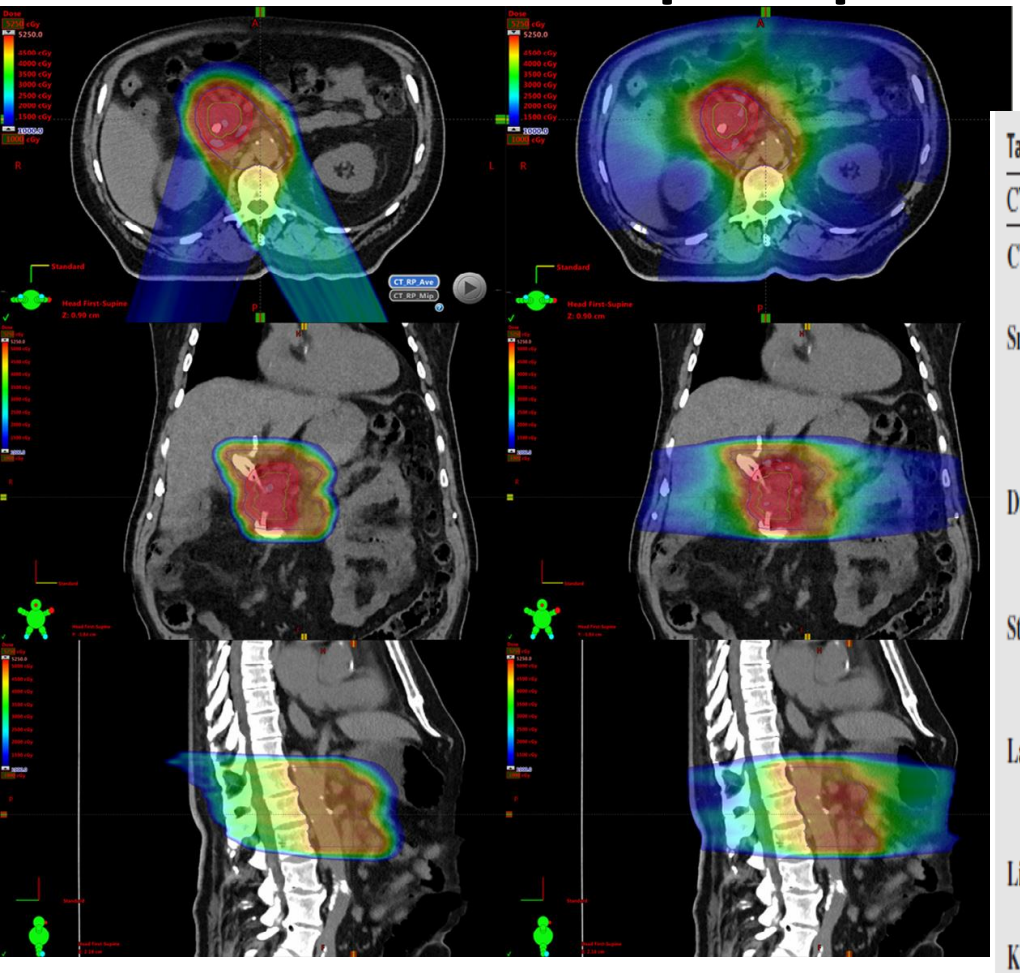


Table 2 Dosimetric comparison of pencil-beam scanning IMPT and VMAT for localized pancreatic cancer

CTV/OAR	DVH parameter (unit)	IMPT Mean (SD)	VMAT Mean (SD)	*P*-value
CTV	CTV45 V95% (%)	100.0 (0.12)	100.0 (0.12)	1.0
	CTV50 V95% (%)	99.9 (0.3)	99.9 (0.3)	1.0
Small bowel	Mean (Gy)	3.7 (3.7)	17.4 (5.6)	< .0001*
	V15 (cc)	55 (75)	292 (311)	.008*
	V30 (cc)	26 (49)	84 (109)	.02*
	V45 (cc)	6 (12)	18 (31)	.05
Duodenum	Mean (Gy)	30.5 (12.0)	38.3 (9.0)	.0005*
	V30 (cc)	41 (20)	51 (25)	.0063*
	V45 (cc)	27 (16)	35 (21)	.0019*
Stomach	Mean (Gy)	5.9 (2.8)	18.9 (3.5)	< .0001*
	V30 (cc)	29 (25)	86 (38)	< .0001*
	V45 (cc)	5 (7)	17 (11)	< .0001*
Large bowel	Mean (Gy)	1.7 (1.3)	15.9 (4.2)	< .0001*
	V30 (cc)	10 (12)	70 (90)	.02*
	V45 (cc)	98 (303)	663 (1125)	.09
Liver	Mean (Gy)	3.6 (2.2)	11.6 (3.2)	< .0001*
	V30 (%)	4.3 (2.9)	8.2 (4.2)	.001*
Kidney	Mean (Gy)	4.1 (1.9)	10.1 (1.6)	< .0001*
	V12 (%)	15.9 (7.5)	36.4 (12.8)	.0001*
	V18 (%)	6.8 (2.9)	7.5 (3.3)	.5
Spinal cord	Maximum (Gy)	39.0 (7.1)	37.4 (4.6)	.54

Advances in Radiation Oncology (2018) 3, 314–321

Dose escalation with Proton Beam therapy

- Improved outcomes with dose escalation
  - 2 yr OS rate 50.8%
  - 2 yr LC rate 78.9%
    - » Hiroshima at al; Radiother Oncol 2019; 136: 37-43
- Improved functional outcomes
  - Less weight loss
  - Improved FACT scores
    - » Jethwa et al. Advances in Radiation Oncology (2018) 3, 314–321

SUMMARY

Summary

- SABR is at least equivalent to conventional chemoRT with current approaches
- Accelerate research to further improve outcomes
  - Dose escalation and newer technologies
  - Options for adding newer agents e.g. Immunotherapy
- There is support from all stakeholders
  - Application for routine commissioning to NHS E has been made

Pancreatic precision RT collaborative

- Prof. Somnath Mukherjee (Oxford)
- Drs. Derek Grose, David McKintosh (Glasgow)
- Dr. Katherine Aitken (RMH)
- Dr. Rebecca Goody (Leeds)
- Dr. James Good (B'ham)
- Dr. Claire Harrison (Belfast)
- Dr. Sarah Gwynne (Swansea)
- Dr. Seema Arif (Cardiff)
- Dr S Falk (Bristol)
- Dr. Ajith Thankamma (Cambridge)
- Dr. Daniel Holyoake, Tom Roques (Norfolk & Norwich)
- Dr. Jonathan Wadsley, Ahmad Sabbagh (Sheffield)
- Dr Andrew Jackson (Southampton)
- Dr. Raj Sripadam (Liverpool)
- Dr. Shamilla Sothi (Coventry)
- Dr. Raj Roy (hull)
- Prof. Maria Hawkins (UCL)
- Dr G Radhakrishna (Manchester)
- …and growing

Acknowledgements

- Patients and carers
- PCUK team
  - Drs C Macdonald
  - Harri Smith and Anna Lakey
- Prf. S Mukherjee, Dr K Aitken et al.
  - Proposal development group for PPP submitted to NHS E for routine commissioning of SABR
- Pancreatic Technical RT teams at the Christie and Leeds