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Precision Radiation Therapy for locally advanced unresectable pancreatic cancer

Outline of session

- Principles and practice of precision RT with a focus on Stereotactic Ablative Body Radiotherapy (SABR)

- Evidence base 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

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- 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 to sensitise to RT or RT to sensitise to drug (e.g immune priming) or Drug to protect normal tissue to allow increase dose to tumour
- Maximal sparing of normal tissue
  - Dose sculpting
  - Knowing when / how to compromise dose / target coverage

Pancreatic RT challenges

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

Principles of radiation therapy in Pancreatic tumours

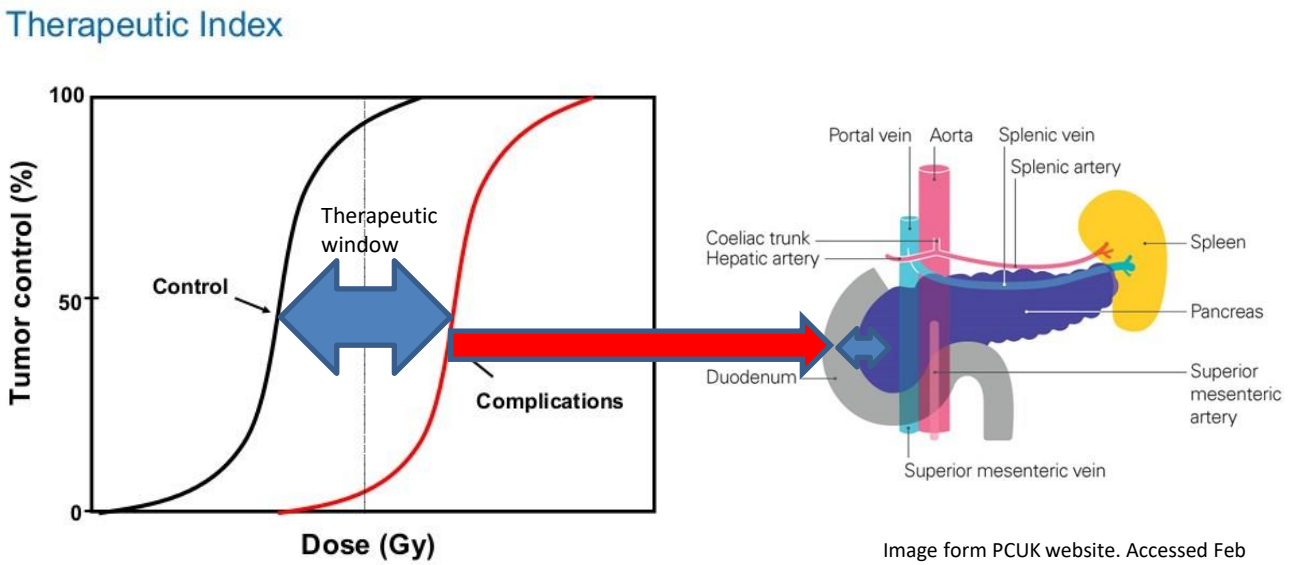

Image form PCUK website. Accessed Feb 2019

Linear Accelerators

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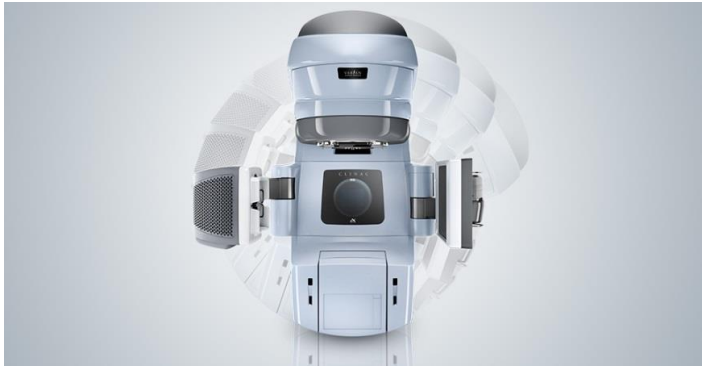


SABR

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

Radiotherapy and Oncology 121 (2016) 86–91

Contents lists available at ScienceDirect

Radiotherapy and Oncology

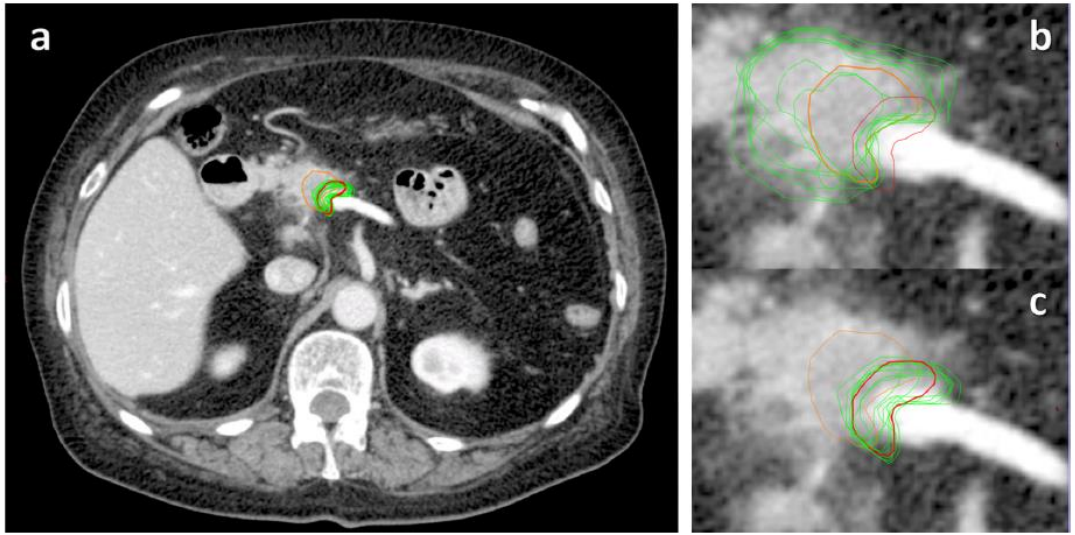
journal homepage: www.thegreenjournal.com

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



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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	0.93–1.04	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	0.333	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

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

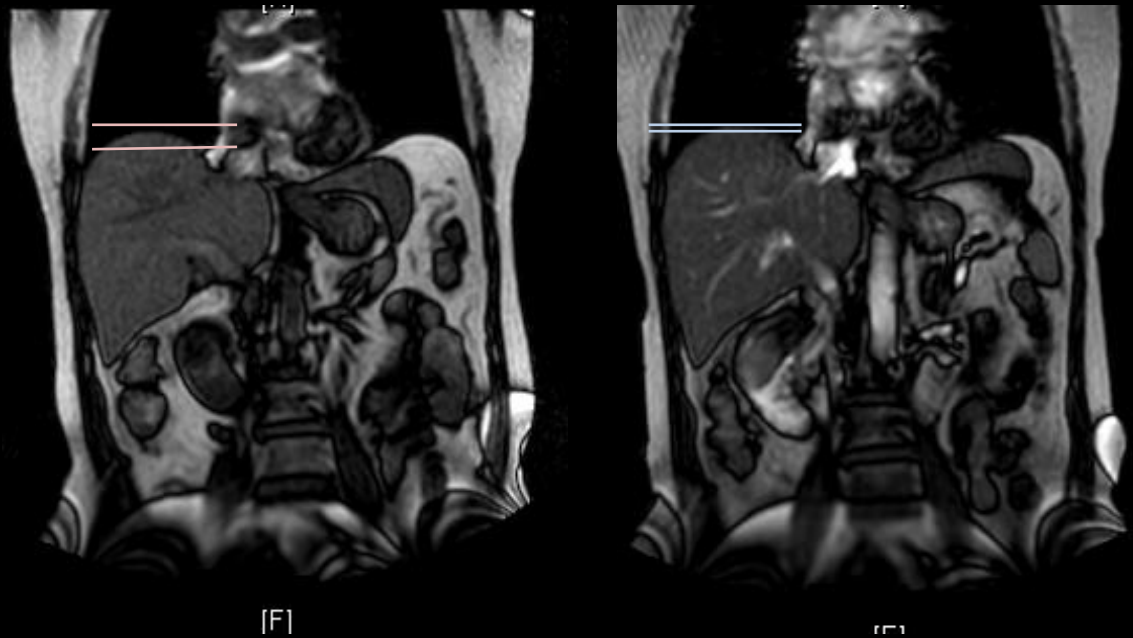
Pancreatic cancer

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



Slide courtesy John Rogers & Lisa McDaid

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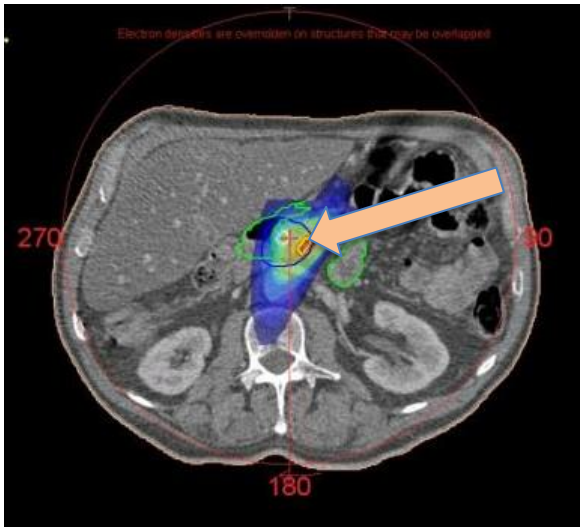
The evidence build

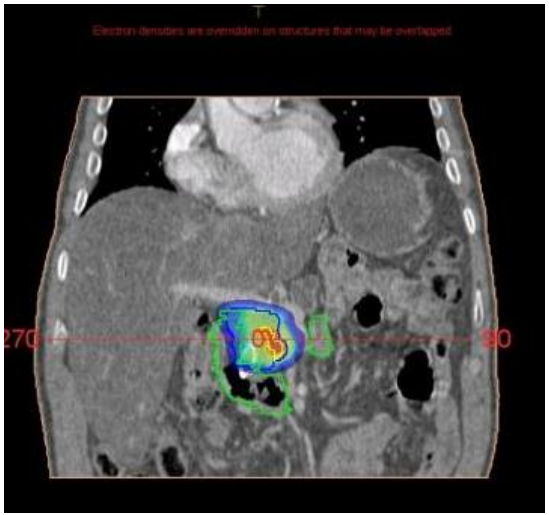
SABR FOR PANCREATIC CANCER

SABR pancreas

- 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

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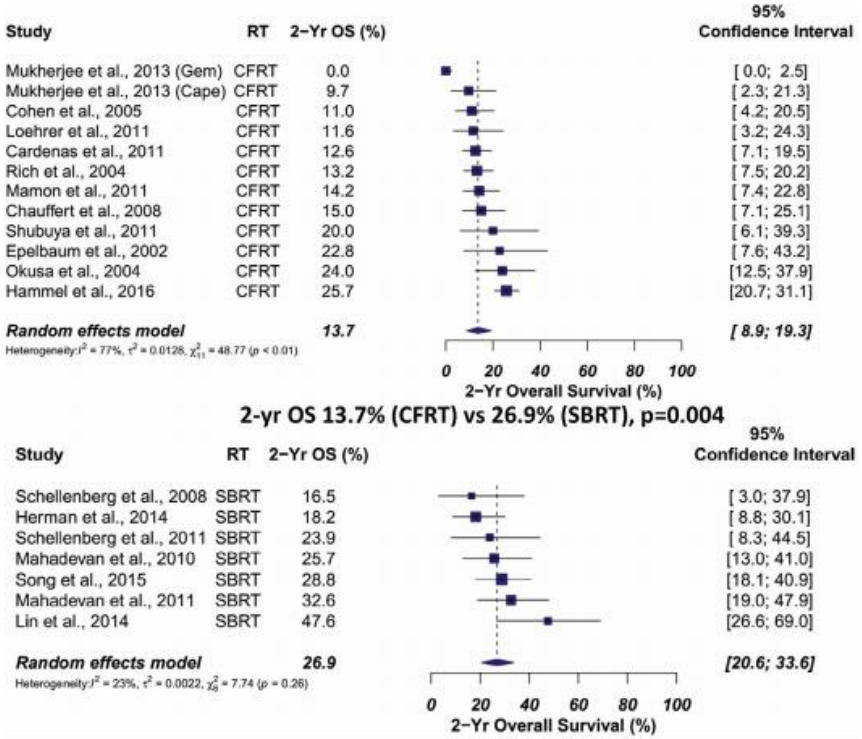
Original Article

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

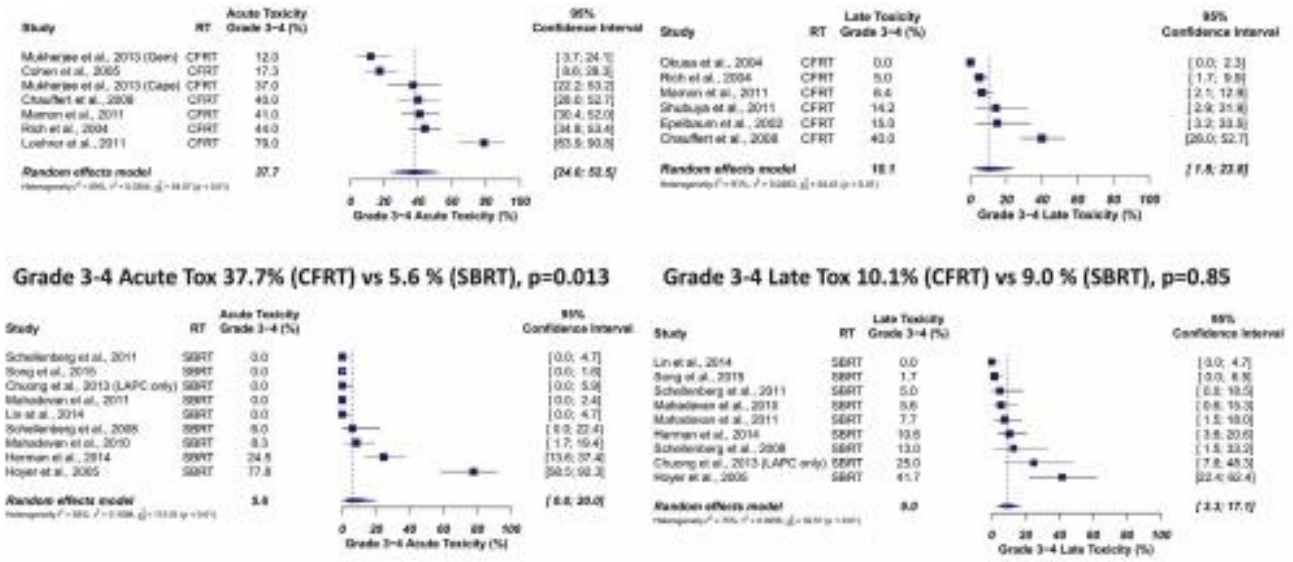
First published: 03 March 2020 | https://doi.org/10.1002/cncr.32756 | Citations: 5

2 year survival



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

Side effect profile



Less acute toxicity and trend towards less late toxicity favouring SABR

Potential benefits of SABR

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- 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. EClinicalMed 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

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LETTER | VOLUME 33, ISSUE 3, E198, MARCH 01, 2021

Stereotactic Ablative Body Radiotherapy for Locally Advanced Unresectable Pancreatic Cancer: Current Views of the Public and Professionals

A. Brocklehurst • C.L. Barker • S. Mukherjee • ... A. Lakey • H. Smith • G. Radhakrishna • Show all authors

Published: November 03, 2020 • DOI: https://doi.org/10.1016/j.clon.2020.10.015 •

Patient- carer perspective – PCUK project

- 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.

  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 and 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 and 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).

RT options

- Dose fractionation schedules

  Selection based on expertise

  Usually adapted based on Organ at Risk tolerances / Treatment volume

Key outcome data SCALOP 2

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	50.4 Gy in 28# (n= 45)	60 Gy in 30# (n= 46)
Induction chemo		
Total no. of patients with grade 1-5 SAEs	20 (44.4)	30 (65.2)
Total no. of patients with SARs/SUSARs	13 (28.9)	22 (47.8)
Patients with grade 3-4 SAEs	13 (28.9)	24 (52.2)
Patients with grade 3-4 SARs/SUSARs	8 (17.8)	16 (34.8)
CRT	(40 started CRT)	(39 started CRT)
Total no. of patients with grade 1-5 SAEs	9 (20)	6 (13)
Total no. of patients with SARs/SUSARs	5 (11.1)	4 (8.7)
Patients with grade 3-4 SAEs	8 (17.8)	6 (13)
Patients with grade 3-4 SARs/SUSARs	**5 (11.1)**	**4 (8.7)**

Events* within 12 months of registration n (%)	50.4 Gy in 28# Arms A+B (n= 45)	60 Gy in 30# Arms C+D (n= 46)
Local progression (with or without metastasis)	**15 (33.3)**	**11 (23.9)**
Metastasis (no local progression)	**11 (24.4)**	**16 (34.8)**
Deaths	**11 (24.4)**	**12 (26.1)**
Evidence of local progression (with or without metastasis)	**7**	**3**
No local progression	**4**	**9**
Deaths before any known progression	**0**	**0**

Slide information courtesy Dr. S Mukherjee

Fractionation schedules

- Chemo radiation

  1.8 – 2Gy per fraction – scalop 2

  ESMO 2022

  28 – 30 treatments over 5.5 to 6 weeks

- 15 fraction option

  As per pre op panc

  Usually concurrent with chemo (capecitabine or gemcitabine)

  Can be RT alone if ultrahypofractionated to 67.5Gy in 15 fractions

- Koay EJ, Hanania AN, Hall WA, et al. Dose-Escalated Radiation Therapy for Pancreatic Cancer: A Simultaneous Integrated Boost Approach. *Pract Radiat Oncol*. 2020;10(6):e495-e507. doi:10.1016/j.prro.2020.01.012
- 6. Colbert LE, Moningi S, Chadha A, et al. Dose escalation with an IMRT technique in 15 to 28 fractions is better tolerated than standard doses of 3DCRT for LAPC. *Adv Radiat Oncol*. 2017;2(3):403-415. doi:10.1016/j.adro.2017.02.004
- 7. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: techniques and results. *Radiation Oncology*. 2019;14(1):95. doi:10.1186/s13014-019-1309-x
- 8. Crane CH. Hypofractionated ablative radiotherapy for locally advanced pancreatic cancer. *J Radiat Res*. 2016;57(S1):i53-i57. doi:10.1093/jrr/rrw016
- 9. Krishnan S, Chadha AS, Suh Y, et al. Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation. *International Journal of Radiation Oncology*Biology*Physics*. 2016;94(4). doi:10.1016/j.ijrobp.2015.12.003

The promise of newer technology

IMPROVING THE THERAPEUTIC INDEX

MR_Linac

Practical Radiation Oncology (2017) 7, 126–136

www.practicalradonc.org

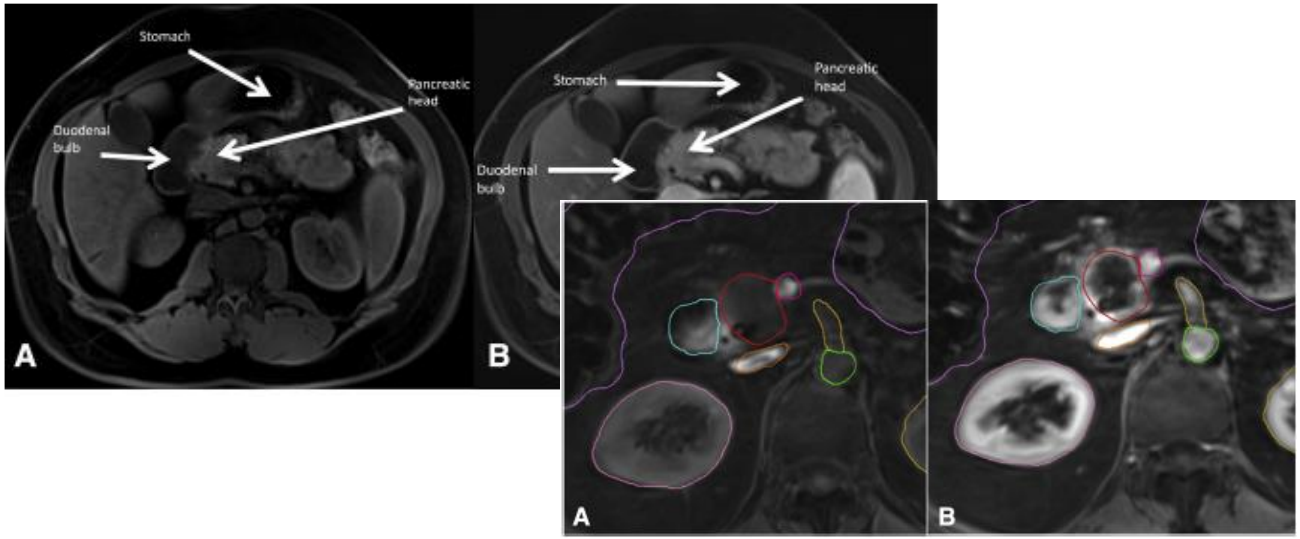
Original Report

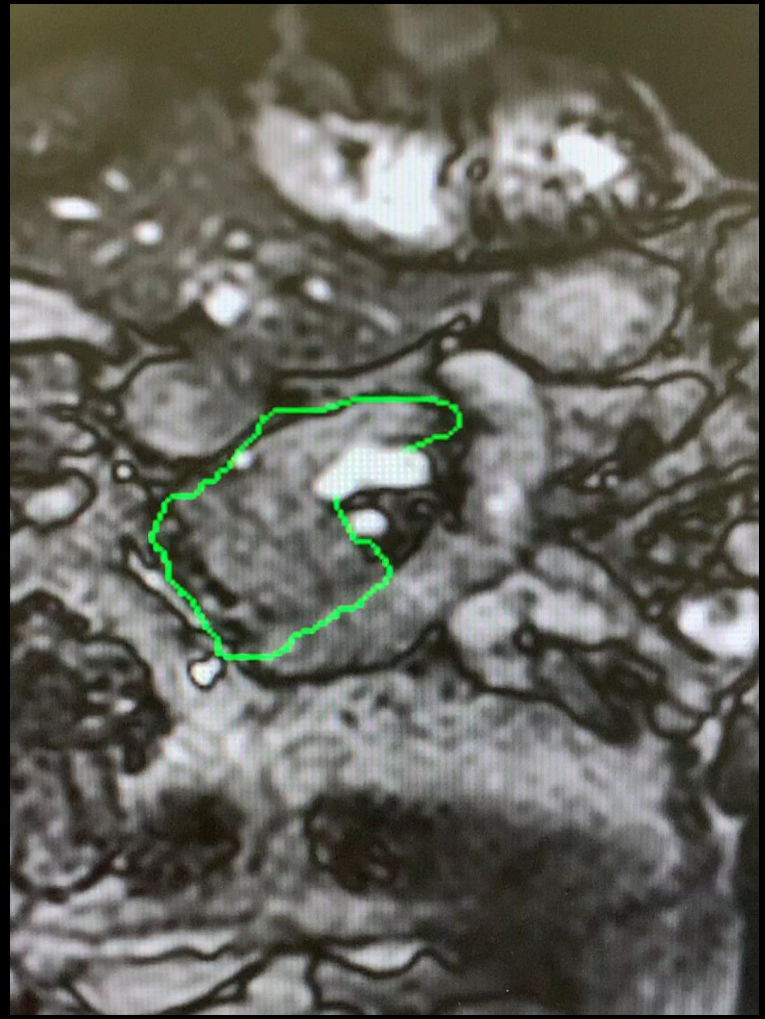
Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer

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,*]

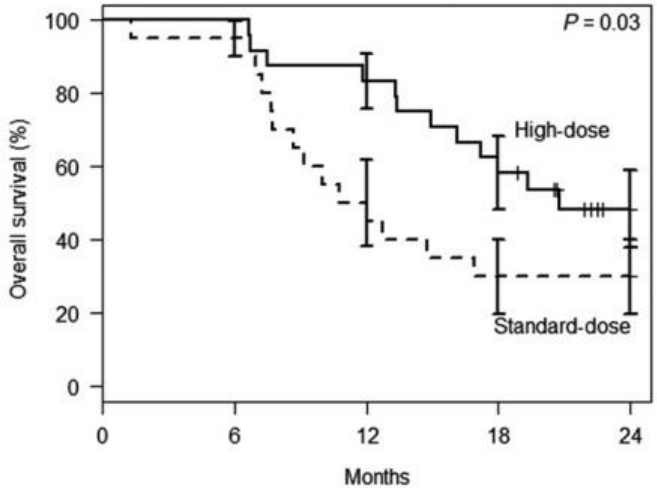
[a]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[b]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin
[c]Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin
[d]Medical Diagnostic Imaging Department, College of Health and Science, University of Sharjah, Sharjah, Dubai
[e]Department of Radiation Oncology, MD Anderson Hospital, Houston, Texas
[f]Department of Radiation Oncology, Royal Marsden Hospital London, England

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%

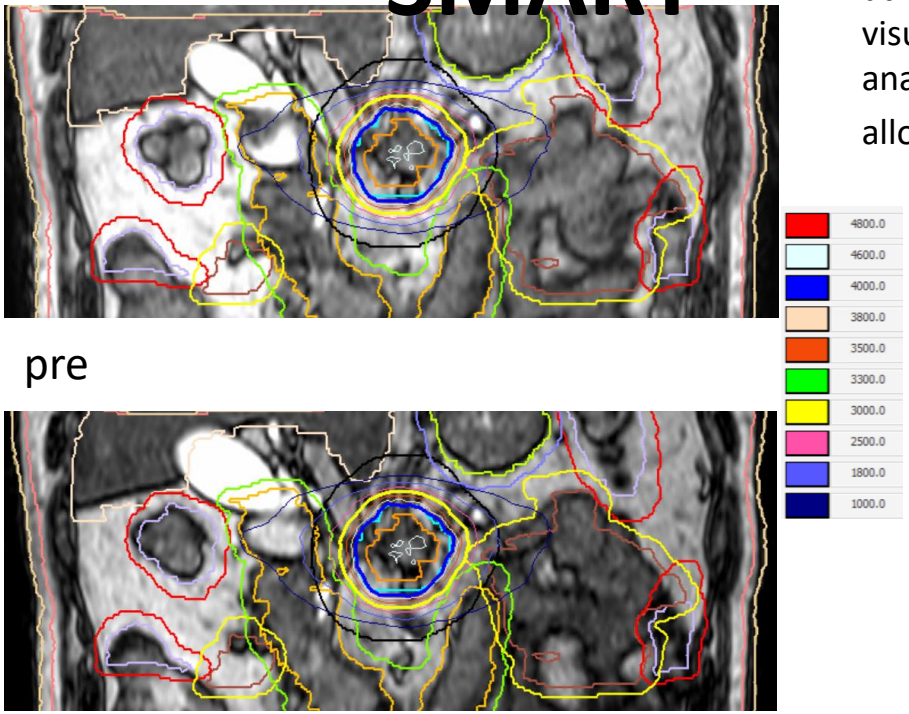
Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. Cancer Med. 2019;8(5):2123-2132.

Stereotactic MR guided Adaptive Radiotherapy
SMART

- Development of Phase 2 studies underway

- Opportunity to evaluate dose escalation with MRgRT

SABR MRg ART and SMART



pre

post

Stereotactic MR-guided online adaptive radiotherapy (SMART) utilises advanced image guidance with sufficient quality to visualise the tumour and OAR and adapt the plan to daily anatomy

allowing for safe dose escalation.

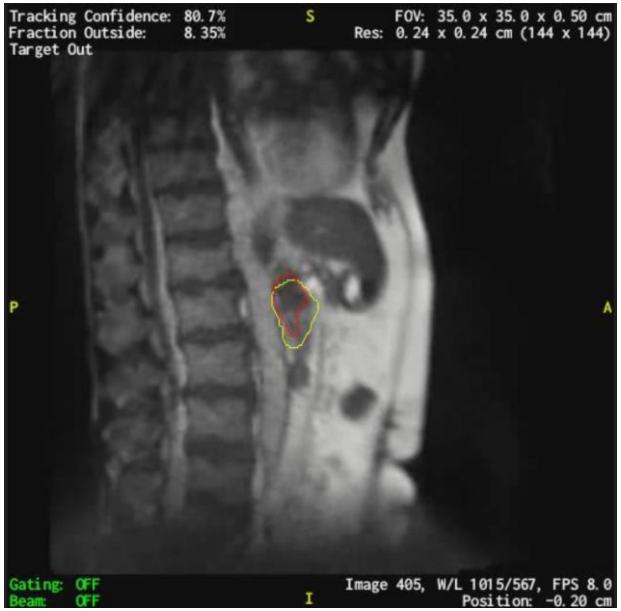


Image courtesy K.Owczarczyk

pro practical radiation oncology ASTRO

BASIC ORIGINAL REPORT | VOLUME 11, ISSUE 2, P134-147, MARCH 01, 2021

Ablative 5-Fraction Stereotactic Magnetic Resonance–Guided Radiation Therapy With On-Table Adaptive Replanning and Elective Nodal Irradiation for Inoperable Pancreas Cancer

Michael D. Chuong, MD • John Bryant, BS • Kathryn E. Mittauer, PhD • ... Vivek Mishra, PhD • Gustavo Luciani, CMD • Alonso N. Gutierrez, PhD, MBA • Show all authors

Open Access • Published: September 15, 2020 • DOI: https://doi.org/10.1016/j.prro.2020.09.005 •

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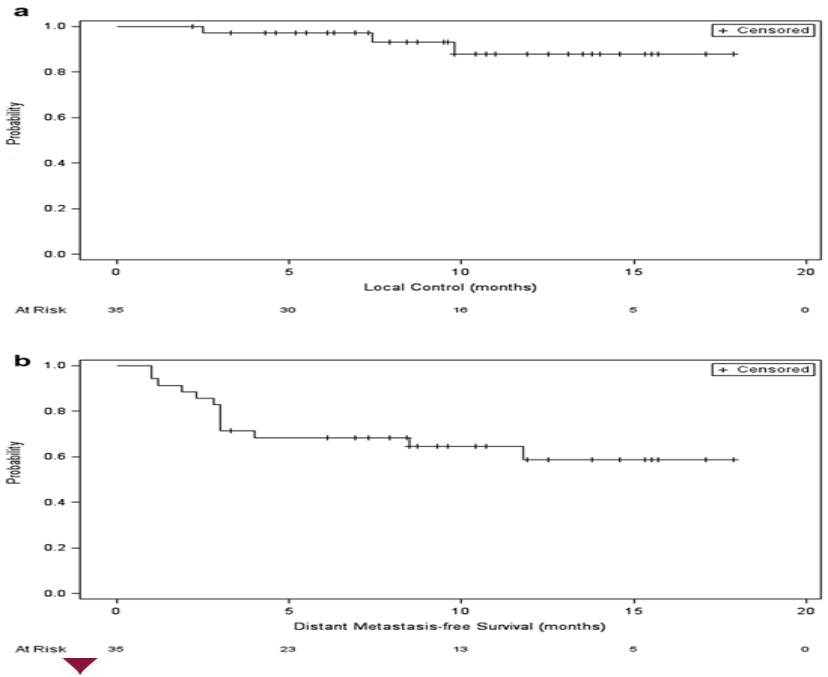

Single inst n= 35

50Gy in 5F ; BED $100Gy_{10}$

> 90% Induction

SACT

G3 acute & late toxicity 2.9%

1 Yr LCR = 87.8%

1 Yr DMFS = 63.1%

I yr OS = 58.9%

1

Roll out of SABR will be underway soon

- First phase within next few months with national roll out from November onwards

2

Access to treatment

- Determine pathways and MDTs aware and refer appropriately

3

Need for clinical trials

- Biomarker driven trials Precision oncology
- integrating technologies , e.g. SMART (Stereotactic MR-guided Adaptive RT) and PBT
  - EMERALD trial Som Mukherjee – oxford
- Accelerate drug-RT studies integrating SABR type options into Systemic treatment and us of newer agents e.g Immuno
  - GRECO – Ajith Thankamma - Cambridge

Acknowledgements

- Patients and carers
- PCUK team

  Dr C Macdonald

  Harri Smith and Anna Lakey

  Abi Lester
- UK HPB Clinical Oncology
- Pancreatic Technical RT teams at the Christie and Leeds