Clinical Oncology:
Establishing novel roles in CCA therapy

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British Association for the Study of the Liver

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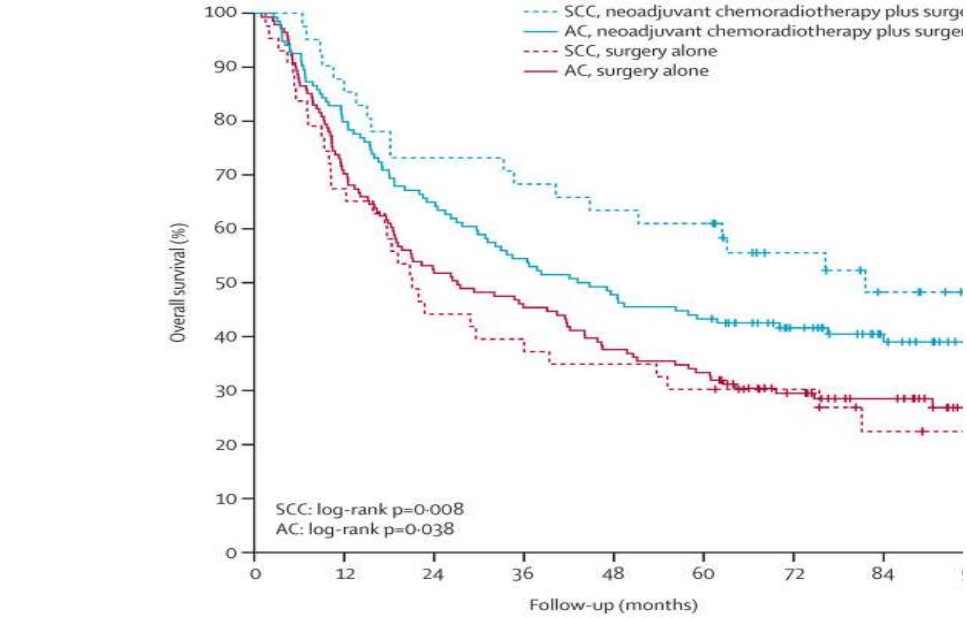
Radiotherapy is just starting to be incorporated in the standard of care in the treatment pathways for GI malignancies

CROSS trial has established the standard for chemoradiation in oesophageal cancer

- RCT comparing CRT+S vs S alone



Number at risk								
SCC, neoadjuvant chemo-radiotherapy plus surgery	41	35	30	28	26	25	17	11
SCC, surgery alone	43	29	19	17	16	13	9	5
AC, neoadjuvant chemo-radiotherapy plus surgery	134	107	87	73	64	58	42	29
AC, surgery alone	141	99	73	64	53	47	32	23
Total	359	270	209	182	158	143	100	68

Median OS

SCC

CRT+S 81·6 mo (47·2-116·0) vs

S 21·1 mo (15·4-26·7)

Adeno

CRT+S 43·2 (24·9-61·4) vs

S 27·1 mo (13·0-41·2)

(HR 0·73 [95% CI 0·55-0·98]; log-rank p=0·038).

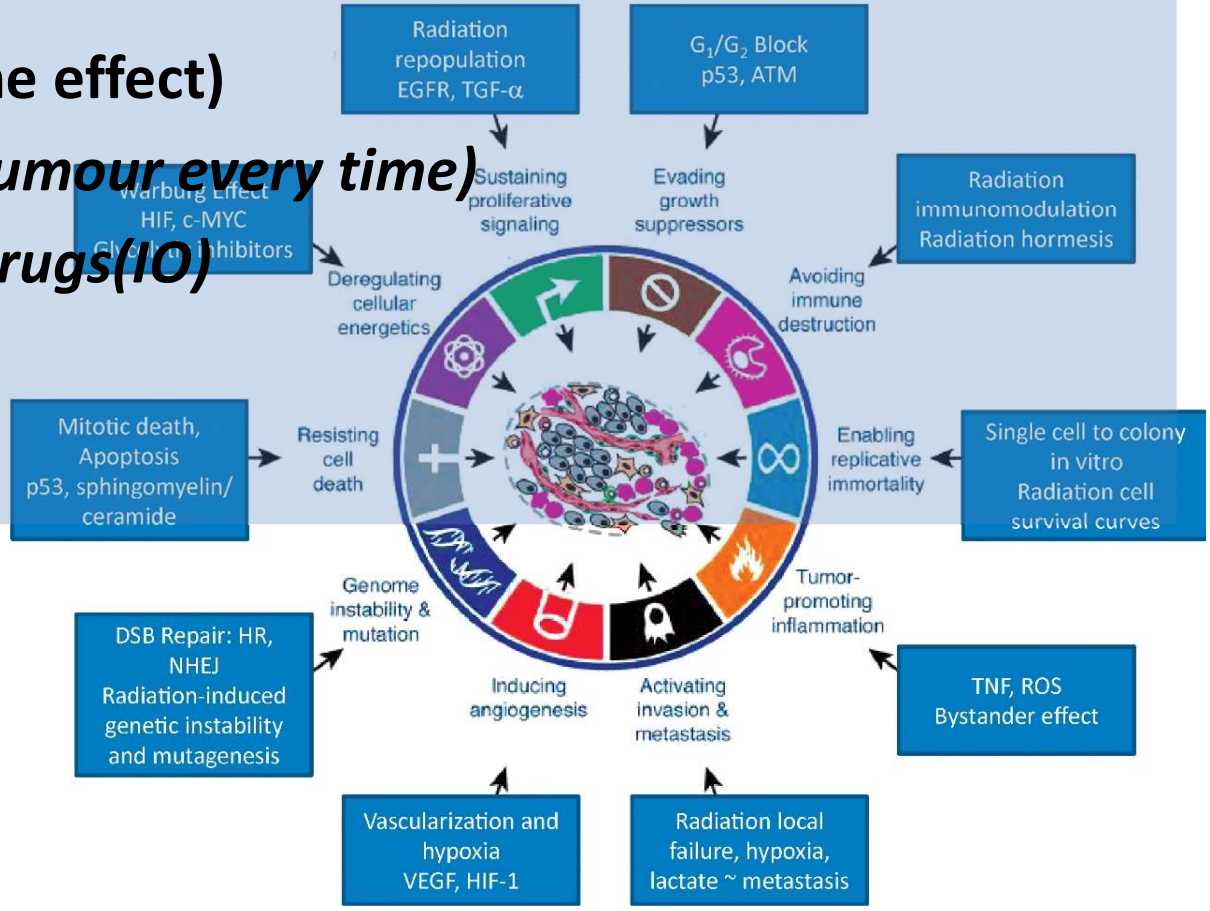
Lancet Oncol 2015

NEJM 2014

MODERN RADIOTHERAPY = physical and biological targeting

delivers a powerful, multi-faceted biological signal that can be personalized:

- **by amount (ie dose)**
- **over time (to vary the effect)**
- ***in space (to hit the tumour every time)***
- ***by combining with drugs(IO)***



Challenges of High Dose Liver (SB)RT

- Tumor visualization is difficult, knowledge of anatomy, and interpretation of multimodality imaging
- Sparing (often diseased) liver parenchyma required
- Proximity of duodenum, stomach colon (critical structures sensitive to radiation)
- Organ motion
  - Respiratory motion
  - Day to day differences
  - Bowel motion

Radiotherapy

- Last 2 decades have seen unprecedented technological advances in radiotherapy (computing, imaging, engineering)

- Stereotactic body ablative radiotherapy
- Combined MRI+ linac
- Proton therapy now can deliver modulated treatment

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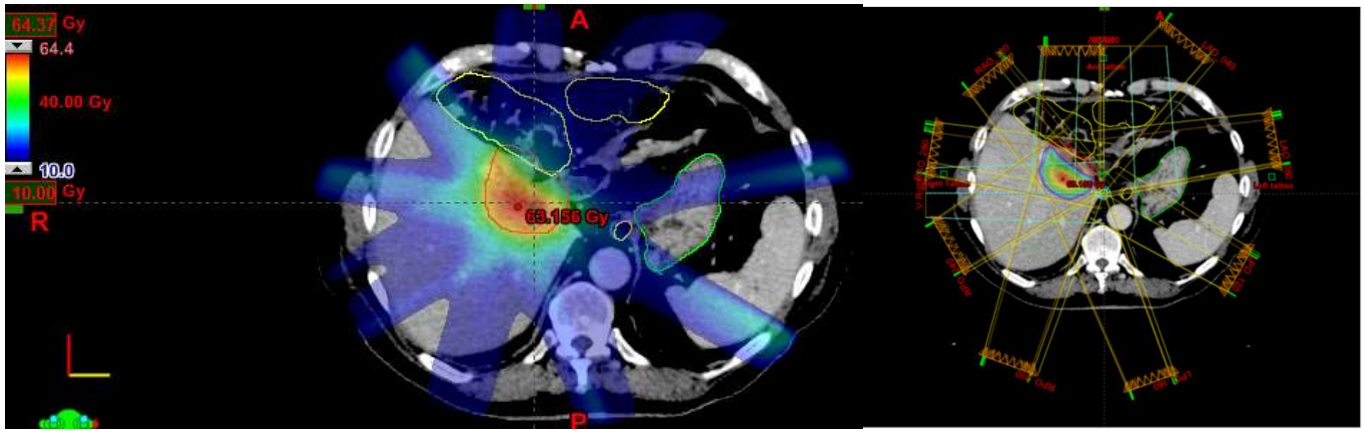
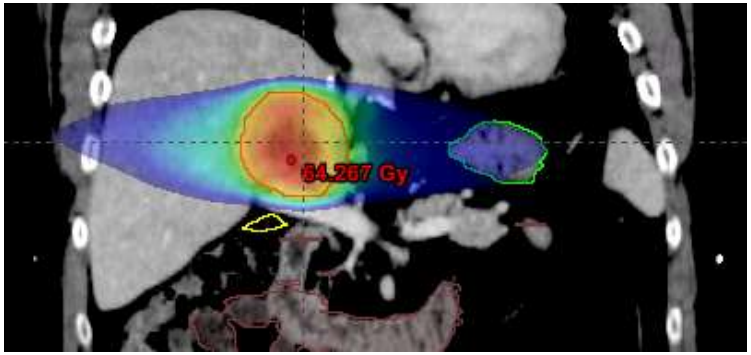
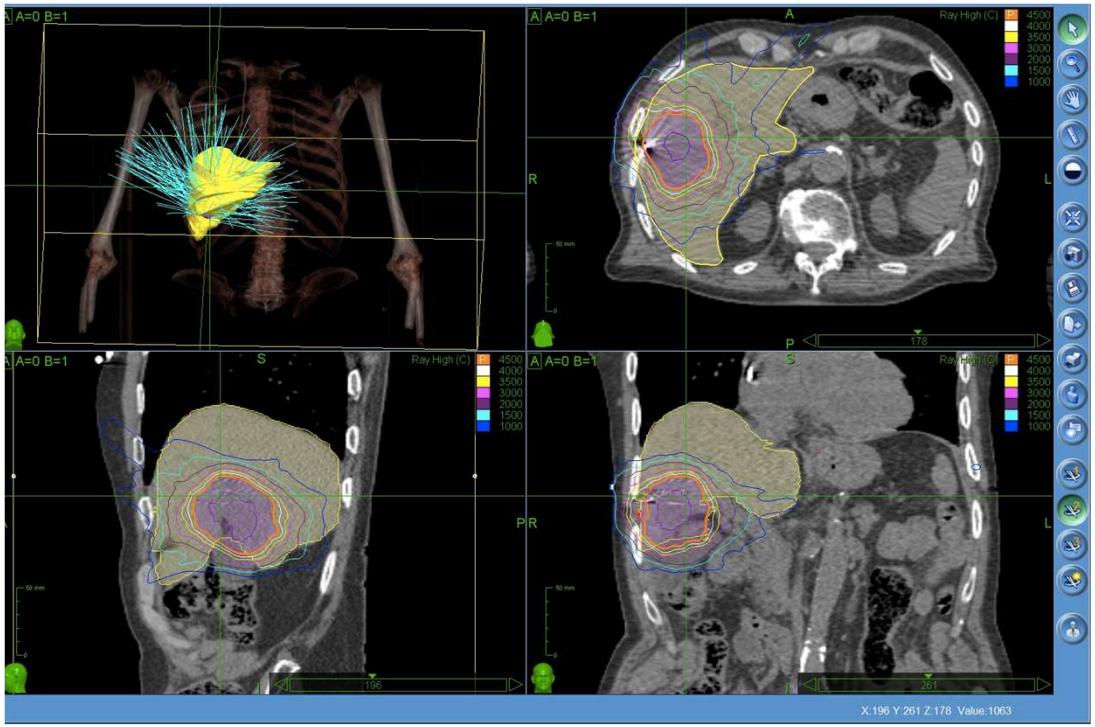

64.37 Gy
64.4
40.00 Gy
10.0
10.00 Gy
A
R
P
63.156 Gy

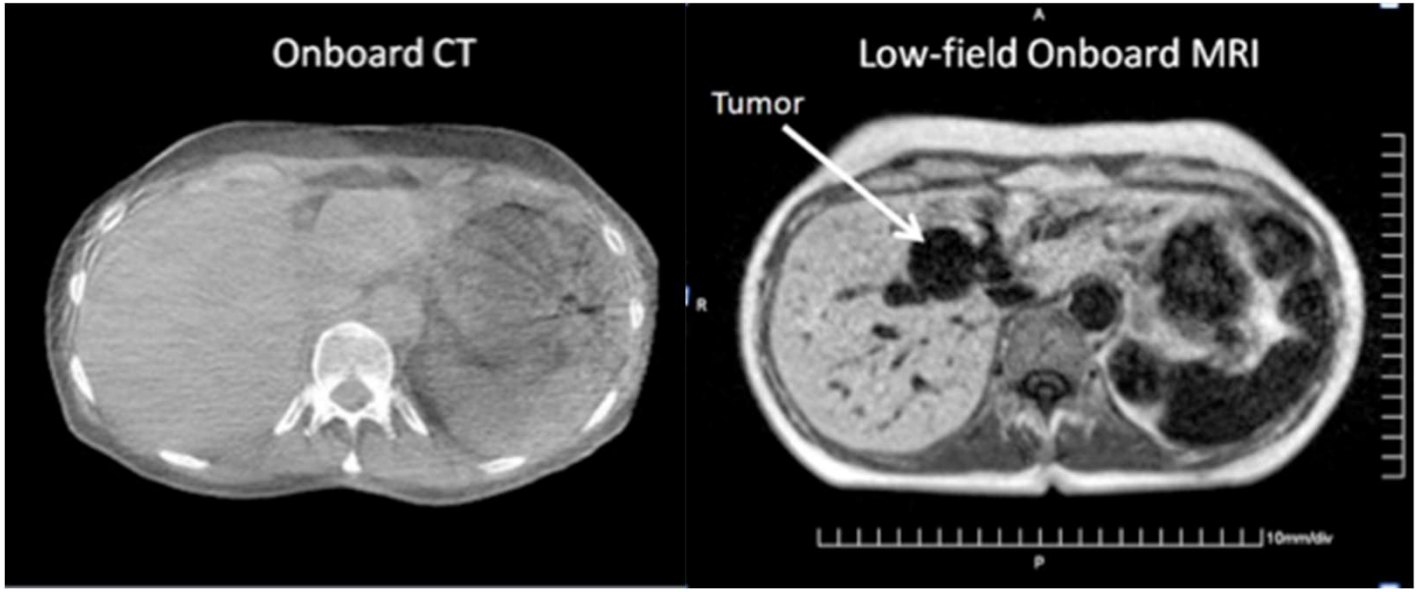

64.267 Gy


A=0 B=1
Ray High (C)
4500
4000
3500
3000
2000
1500
1000
A
R
L
P
S
178
196
261
X:196 Y:261 Z:178 Value:1063

Use of multimodality imaging to visualise the tumour on the linac

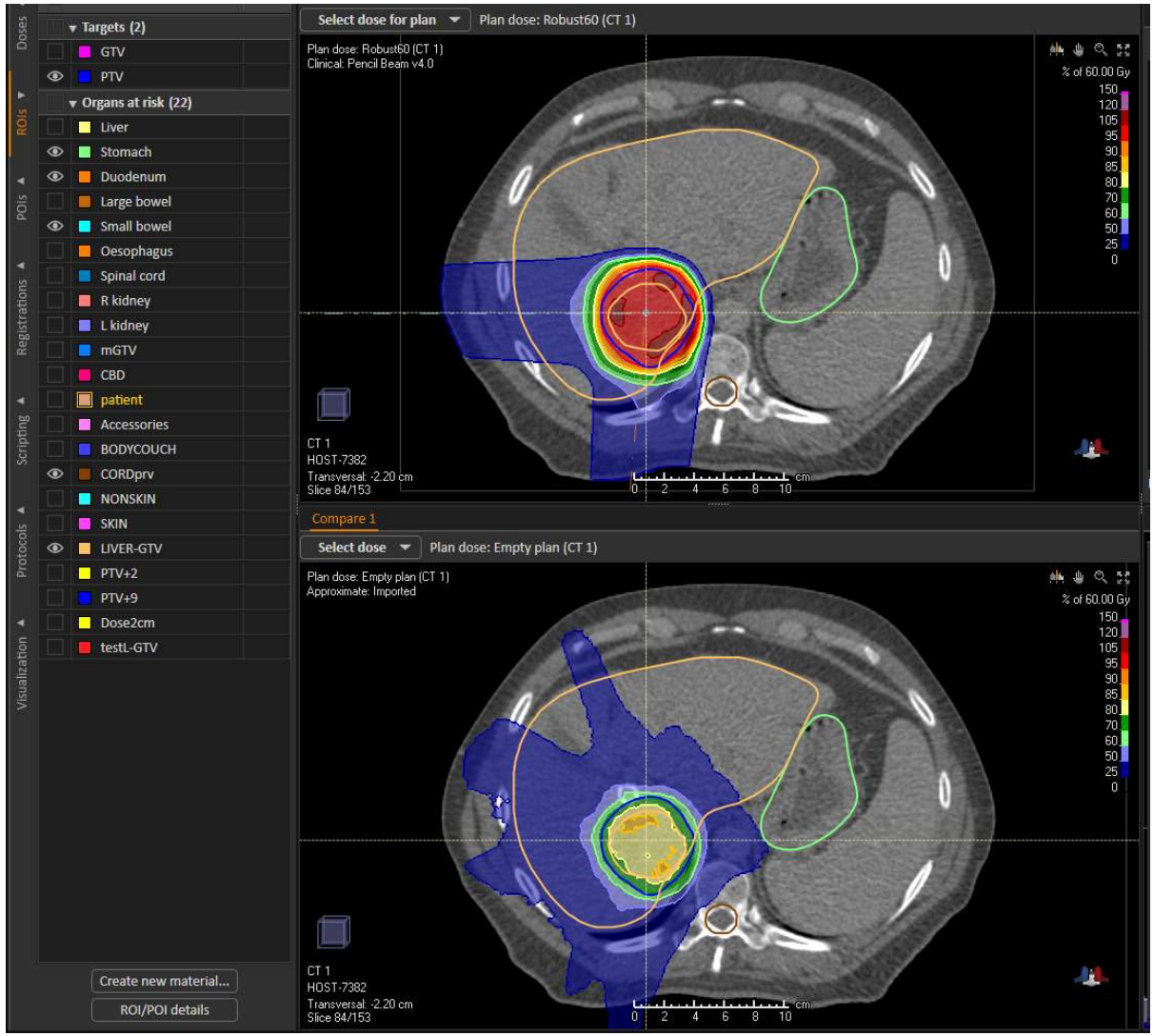
- +computing power= treatment of the day

MRIdian MRI



Particle therapy

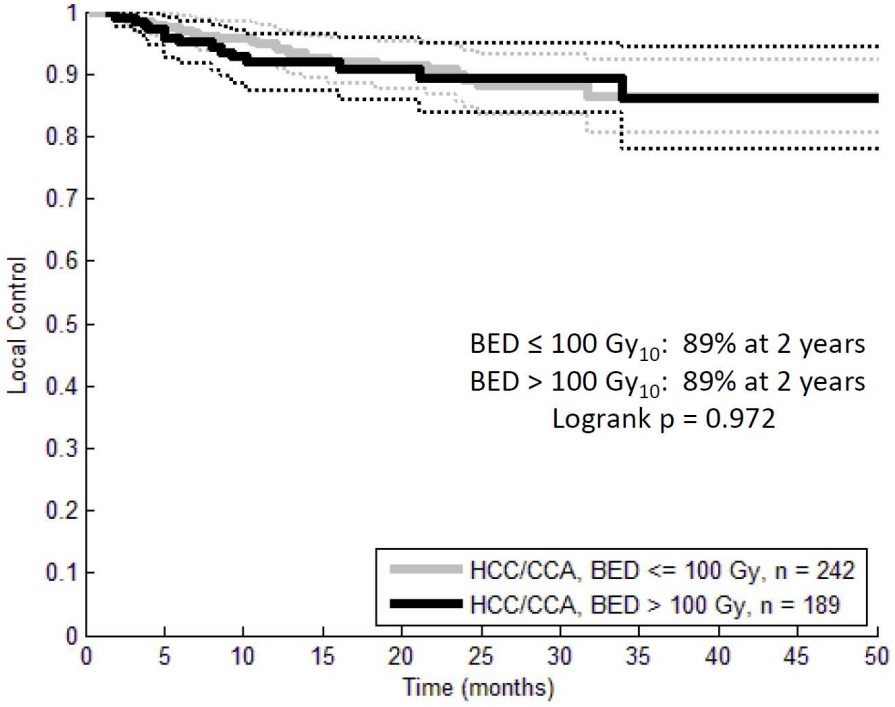
Protons are now available in the UK



Protons

Photons

Primary Liver Tumours:
Local Control of 89% at 2 years
~100Gy Biologically effective dose
n=431 +SBRT



Toxicity:
Grade 3 liver enzymes=6%
Grade 2 general GI tox=36%

Radiation Therapy

- External Beam Radiation Therapy *is rarely used in the UK*.

Some progress with RT

- In 2014 1 UK centre was using RT in locally advanced inoperable cholangiocarcinoma
- 2018- 20 centres have been credentialed to deliver SBRT for cholangiocarcinoma part of ABC07 trial

2018 July J Bridgewater asked sites involved in ACTICCA study14 centres have answered

Question 1a: Is chemo-radiotherapy used in your centre in adjuvant setting?

13/14 do not use CRT in this setting

Question 2a: Are you interested in participating in the ACTICCA-RT sub-study?

11/14 yes, 1 maybe (if we show them the rationale) and 2 no

Levels of evidence for the use of radiotherapy

Setting	Randomised	Phase II single arm
Perioperative (transplant)	no	Institutional (Mayo- transplant)
postoperative	no	Phase II SWOG
Locally advanced	no	Phase II Boston/MDACC
metastatic	No	no

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Levels of evidence for the use of radiotherapy

Setting	Randomised Ongoing studies	Lead
Perioperative (transplant)	1 RCT TRANSPHILL	French
postoperative	In develop ACTICCA-RT	UK colab DE
Locally advanced	1RCT ABC07	UK
metastatic	1.5 RCT SI RCCA	Industry Open in UK

Progress in RT

- field of radiobiology small size and seems to be integrated within larger scientific disciplines
- need a continued commitment to mechanistic discoveries
- need development of drugs to overcome radioresistance
- need to study complex interplay between the host immune system and irradiated tumour
- Understand and use existing biomarkers
- Collaborate and learn from other specialties

Biological questions relating to RT

- identification molecular signatures/biomarker where a rationale combination of RT and could be beneficial ? (e.g. DDR pathway, immune, high tumour mutational burden)
- Identification of a “low-metastatic potential” tumour that would benefit of ablative RT treatments
- RT to produce tumour circulating antigens therefore enhancing IO

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“Physical” questions relating to RT

~30% of resected patients have +ve margins

Would adjuvant RT “rescue” R1 margin

(in addition to systemic treatments)

Could RT preoperatively “sterilise” margins ?

(but would surgeons accept the help?)

? Define borderline resectable cholangiocarcinoma cohort

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Future considerations

- active systemic therapies become better to target disseminated microscopic disease,

therefore local therapies will play an increasingly important role

- Rationally incorporate RT in current treatment paradigms
- Increase efforts in preclinical radiobiology setting
- Predictive and prognostic biomarkers for patient and tumour stratification

Randomised trials testing RT non metastatic setting

- Liver Resection Vs CRT +Transplant Hilar CC

[TRANSPHILL study NCT02232932]

- Addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced biliary tract cancers ABC07 study EudraCT 2014-003656-31
- *in development ACTICCA RT (embedded RCT for R1)-*

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Randomised trials involving RT metastatic setting

- 1L SIRT + CIS-GEM Vs CIS-GEM Unresectable Intrahepatic Cholangiocarcinoma (SIRCCA NCT02807181)
- 2L Nivolumab +/- Ipilimumab in Combination With Radiation in metastatic pancreas and cholangio (RT 15Gy 1F on D1) MSD+Danish centre CheckPAC study NCT02866383

SWOG S0809 Gem-Cape then capeRT
Phase II, single arm, multicentre,

- EHCC or GBCA (but not ampullary cancer) after radical resection, with pathologic stage T2-4 or N1 or positive resection margins.

- Results would be considered promising if the 95% CI for 2-year OS estimate excluded a rate ≤45%and if the stratum-specific point estimates were ≥65%forR0and ≥45% for R1.

Ben-Josef, E., et al., SWOG S0809:. J Clin Oncol, 2015. 33(24): p. 2617-22.

- 4 cycles of Gem-Cap, then CRT 45Gy/25

SWOG S0809 Gem-Cape then capeRT

79 eligible patients (R0, n = 54; R1, n =25; EHCC, 68%; GBCA, 32%) were treated (86% completed), acceptable toxicity

2 yr DFS 52% (met threshold of activity)

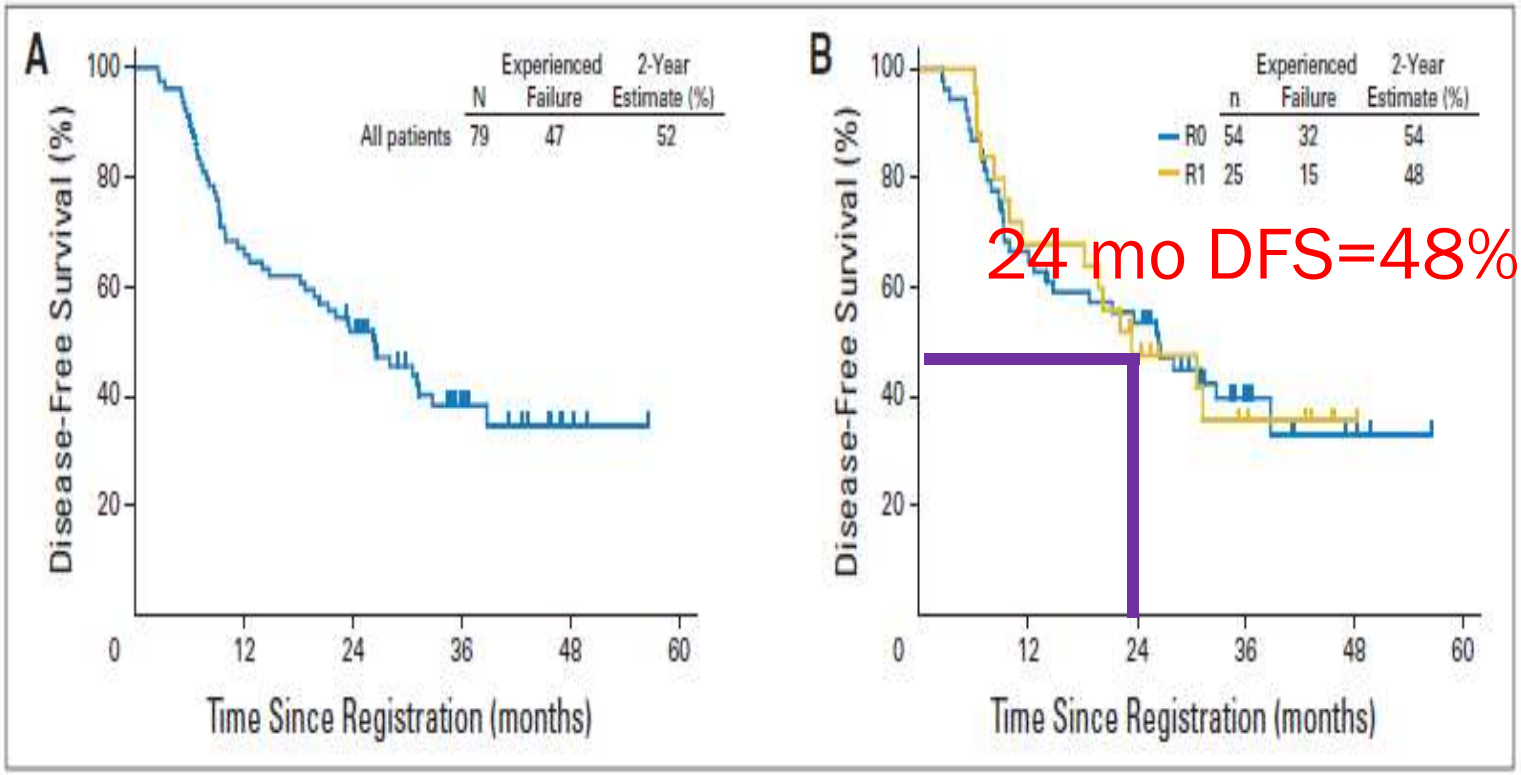


Fig 2. Disease-free survival (A) in all patients and (B) by resection margin; 2-year estimate was 52% for all, 54% for R0, and 48% for R1 patients (not significantly different).

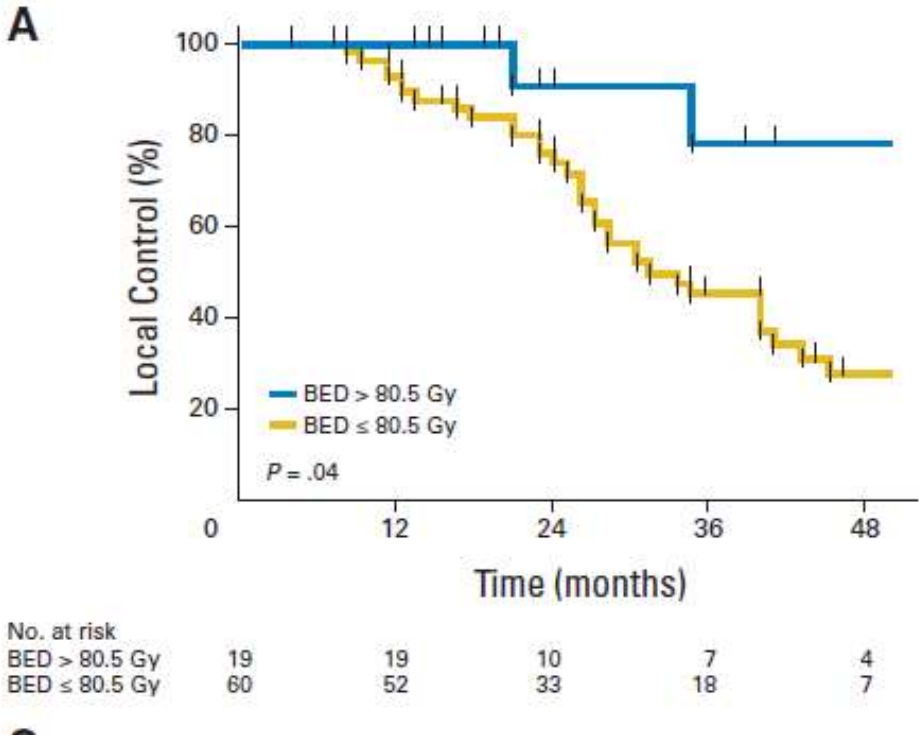
Ben-Josef, E., et al., SWOG S0809:. J Clin Oncol, 2015. 33(24): p. 2617-22.

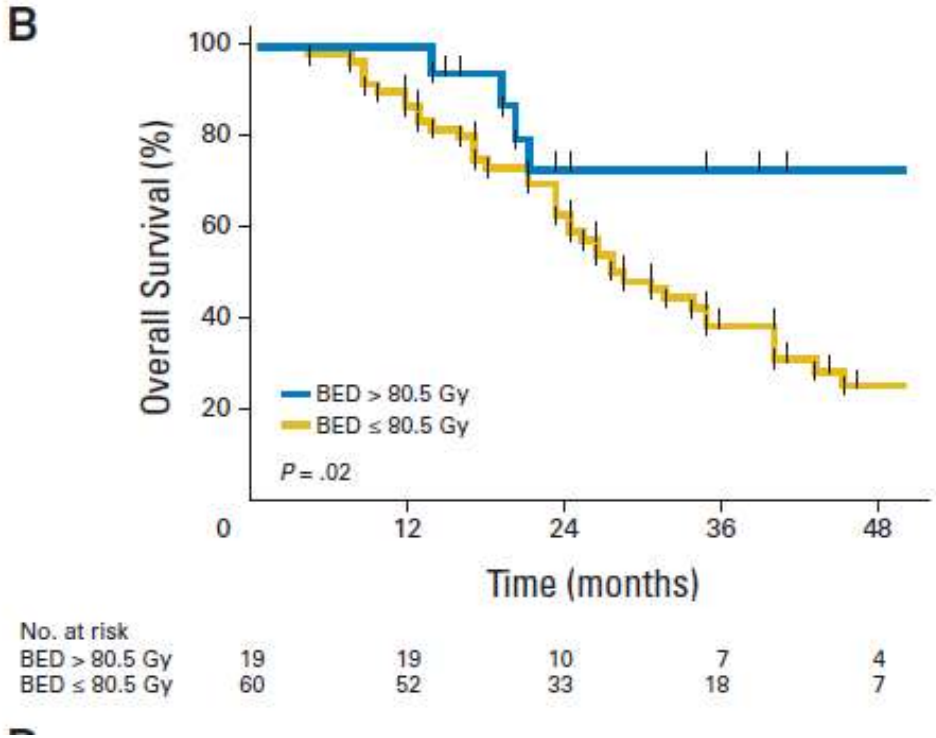
MDACC: Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma:

- 79 pt 2002-2014, retrospective
- median tumor size 7.9 cm (range, 2.2 -17 cm).
- 70 (89%) received systemic chemotherapy before RT.
- RT doses median, 58.05 Gy(35-100) in 3 to 30 fractions median biologic equivalent dose (BED) of 80.5 Gy (range, 43.75 to 180 Gy)

- Median FU=33 months (range, 11 to 93)
- Median OS=30 mo, 3 year OS=44%
- Higher doses correlated with an improved LC, and OS

Crane JCO 2015


A
100
80
60
40
20
0
Local Control (%)
BED > 80.5 Gy
BED ≤ 80.5 Gy
P = .04
12
24
36
48
Time (months)
No. at risk
BED > 80.5 Gy 19 19 10 7 4
BED ≤ 80.5 Gy 60 52 33 18 7

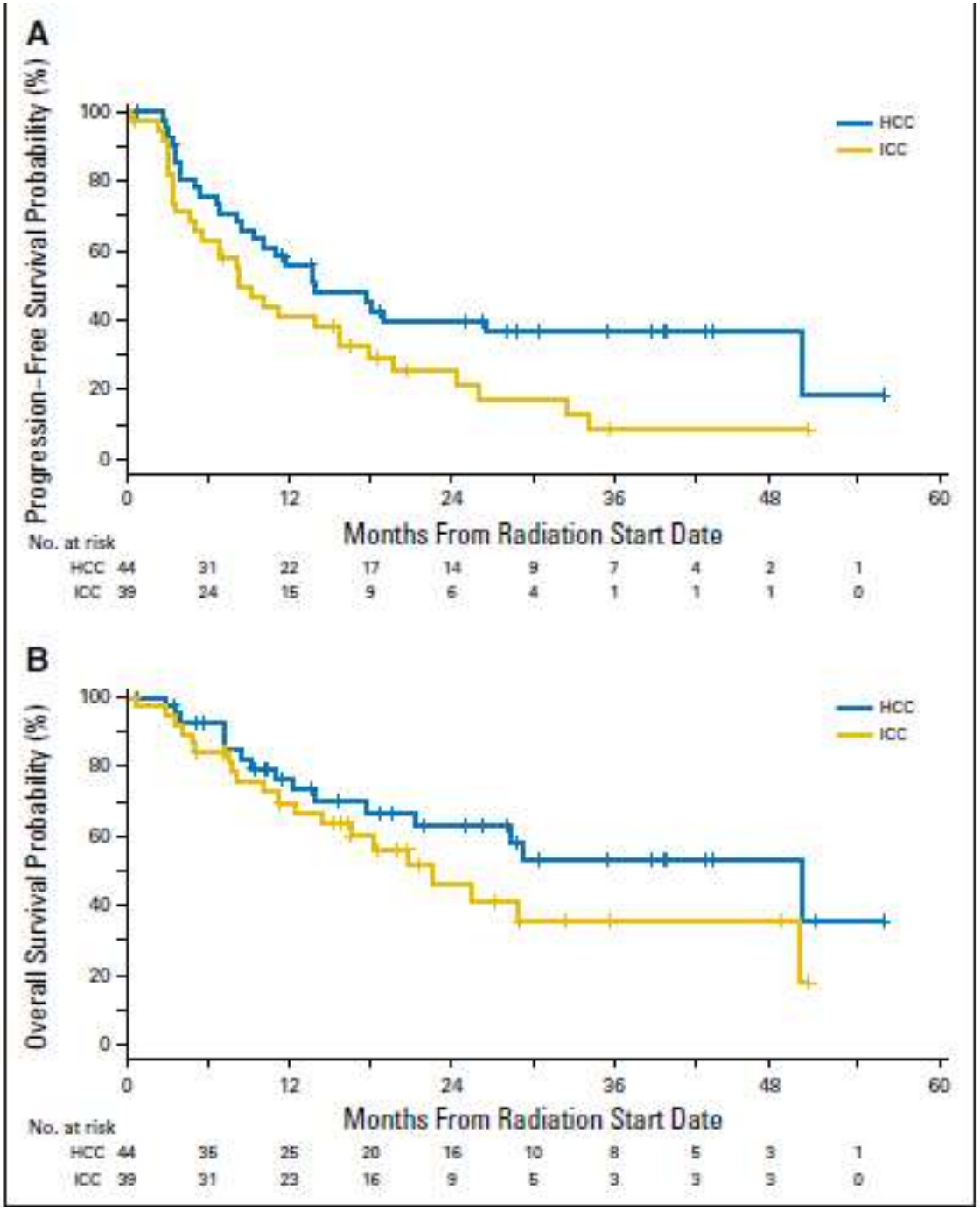

B
100
80
60
40
20
0
Overall Survival (%)
BED > 80.5 Gy
BED ≤ 80.5 Gy
P = .02
12
24
36
48
Time (months)
No. at risk
BED > 80.5 Gy 19 19 10 7 4
BED ≤ 80.5 Gy 60 52 33 18 7

Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

- 92 patients- 83 evaluable
- biopsy+ve HCC (44) or ICC (37), PS=0-2, Child-pugh A (80%)+B
- 67.5GyE in 15 fractions (protons)
- 61% of ICC patients had prior treatment
- Median tumour dimension was 6 (2.2.-10.9) cm (ICC) and 5 cm (1.9-10cm) for HCC

- Median dose delivered was 58GyE
- With a median FU 19.5 months,
- LC rate at 2 years was 94.8% for HCC and 94.1% for ICC.
- The overall survival rate at 2 years was 63.2% for HCC and 46.5% ICC.

Hong JCO2015



OS at 2 years

63.2% for HCC

46.5% ICC