Where are we with radiotherapy for biliary tract cancers?

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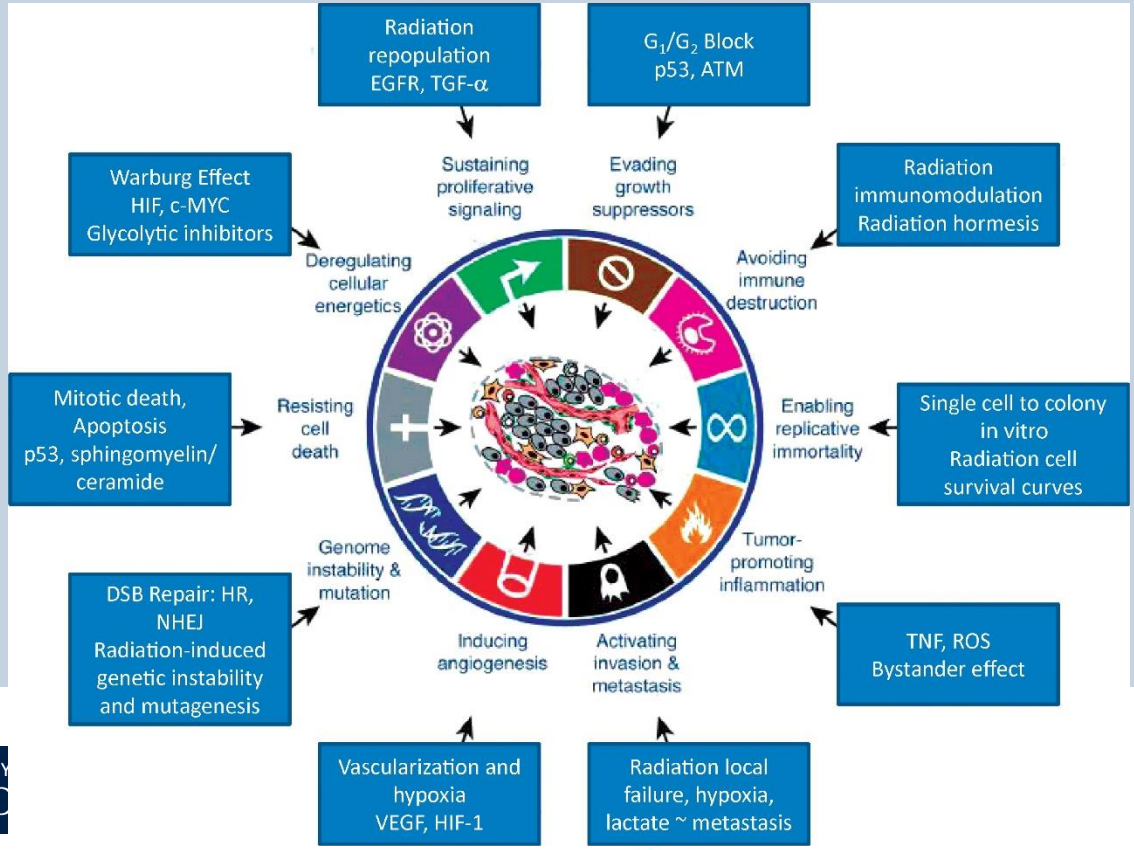
- Biliary tract cancer are a diverse group of disease and incidence is increasing
- The outcome of biliary tract cancers are poor
- The standard of care (for locally advanced cancers) has not really changed since ABC02
- Treatment for unresectable locally advanced BTC patients has not been defined
- Precision radiotherapy looks promising but high quality evidence is lacking

MODERN RADIOTHERAPY
combines physics and biology
delivers a powerful, multi-faceted biological signal that can be personalised:

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



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Radiotherapy in cholangiocarcinoma possible indications

- Curative setting
  - Pre-transplant
  - Post-operative
  - Definitive setting
- Metastatic setting
  - Oligometastatic disease
  - Stimulate immune response
  - Palliative

Challenges of High Dose Liver (SB)RT

- Tumor visualization is often difficult
- Need to spare (often diseased) liver
- Proximity of duodenum, stomach, colon (also sensitive to radiation)
- Organ motion
  - Respiratory motion
  - Day to day differences
  - Bowel motion

Novel radiation techniques developments-opportunities for cholangiocarcinoma

- SBRT (stereotactic body ablative radiotherapy)
- Proton therapy
- +immune therapy (IO+RT combinations)

Radiation Therapy in cholangiocarcinoma

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

Definitions

Stereotactic	*multiple radiation beams*
Ablative	*that cause tumour necrosis*
Body	*in extra-cranial locations*
Radiotherapy	*at high doses per fraction*
SBRT	Stereotactic Body RadioTherapy
Radiosurgery	*intracranial sites, one fraction*
CyberKnife	*one way of delivering the above*
VMAT	*volumetric arc therapy – another way*

Standard RT vs. Stereotactic RT

Standard Radiation Therapy	Stereotactic Radiation Therapy
Delivered over 5-6 weeks, Mon-Friday	Delivered over few days
Low doses of RT/day (1.8 – 2 Gy)	High doses of RT/day (5-30 Gy)
Large margins	Small margins
Usually combined with chemotherapy	No concurrent therapy
Normal tissue can repair	More difficult for normal tissues to repair the damage
Shorter treatment times per day (10-15 minutes)	Treatment times sometimes >1 hour
Acute > Chronic toxicity	Chronic > Acute Toxicity
Less Convenient (worse quality of life)	Better quality of life
Good long term data	Less data

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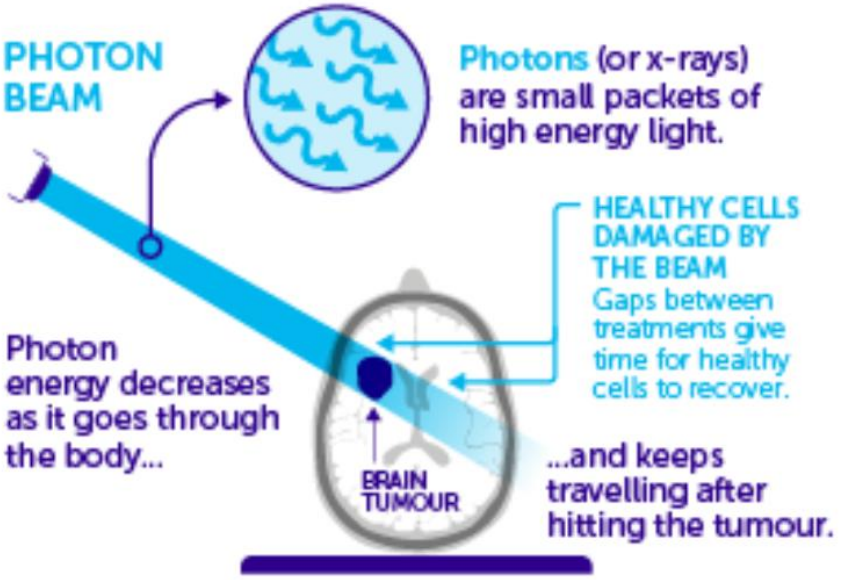
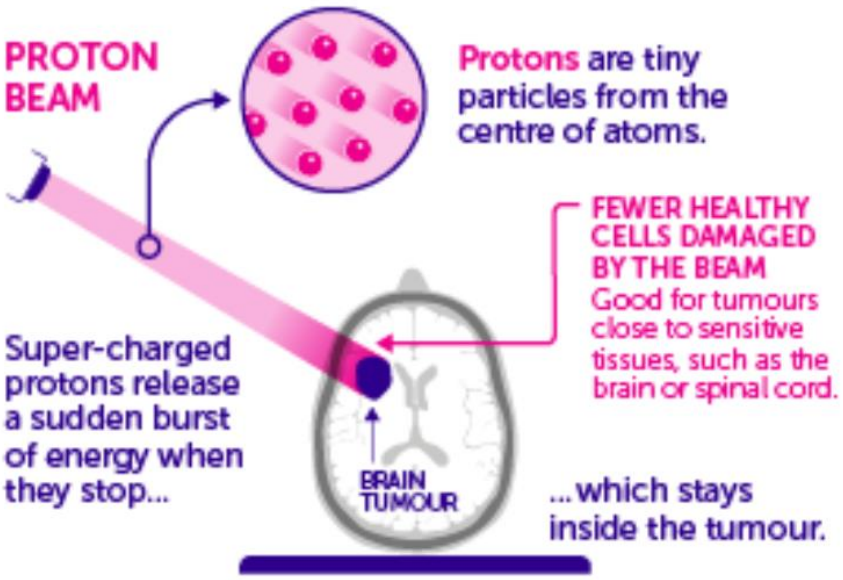
PHOTON AND PROTON RADIOTHERAPY
WHAT'S THE DIFFERENCE?

Radiotherapy targets tumours with a beam of energy which damages DNA and kills cancer cells.





LET'S BEAT CANCER SOONER
cruk.org

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What are the options in non-metastatic disease?

- Surgery has been the cornerstone of curative therapy
  - In surgical patients median OS=21mo; OS 3yr=40%,5 =35%,

  Median time to recurrence 14mo

  Survival better if R0 vs R+: 5 yr survival rates of 19-47% vs 0-12%

- following liver transplantation, 5-year OS 30%,
- 5yr OS ~71% with the addition of neoadjuvant therapy chemoradiation prior to liver transplant in a highly selected population able to complete multimodality therapy

Wong JCO 2013, Nathan 2007, Kloek 2008, rosen 2012

Locally Advanced Biliary Tract Cancer
Treatment options

Optimal strategy continue to evolve: treatment options include

- Clinical trial
- Multiagent chemotherapy gemcitabine/platinum based
- Local ablative treatments e.g. radiation
- Best supportive care

biological therapies are promising but still under investigation

- Personalised treatments are still under development

- Should we consider radiotherapy for non-operable non metastatic lesions?

ABC-02 study defines chemo standard in BTC

RCT Cis-Gem vs. Gem n=410 recruited Feb 2002- Nov 2008
in locally advanced + mets

- median OS 11.7 mo vs. 8.1mo HR=0.64, 95%CI 0.52-0.8 p<0.001
- Median PFS= 8.0mo vs 5.0 mo p<0.001

- 78 (20%) pt with locally advanced disease recruited in the study.
- 68/78 (87%) had PR+SD after 8 cycles of chemotherapy
- cis-gem arm, 39/44 (88%) had PR+SD.

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Valle NEJM 2010

Rationale to use RT in cholangiocarcinoma

- **Patterns of relapse following surgery**

  - MSK retrospective review 90-06 82/270 resection
  - Median disease specific survival 26 mo, 62% recurrence within liver remnant

  - S Korea retrospective review 95-2012 153 IHCC resections
  - 93 patients recurred, 60 in the liver remnant within 2 cm of resection margin

  - BILCAP data 128 patient had R1 and 50% of patients with R1 had local recurrence only

Gil 2015

Rationale to use RT in cholangiocarcinoma

- **Evidence regarding radiosensitivity in cholangiocarcinoma**

  - Retrospective 12 transplant centres 287 pt CRT 45Gy+20Gy brachy boost + liver transplant,
  - at explant 54% no tumour seen as a result of complete radiation induced necrosis (but some of them did not have positive histology confirmed)

  - RT independently predicts outcome in perihilar cholangio following neoadjuvant chemoradiation + transplant and can stratify patient prognosis

- **Continuing local disease after chemo in locally advanced disease ABC02**

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Lehrke 2016

Direct evidence of radiation effect

- Prospective and retrospective

Summary SBRT # (1-6# at ~10Gy/#)

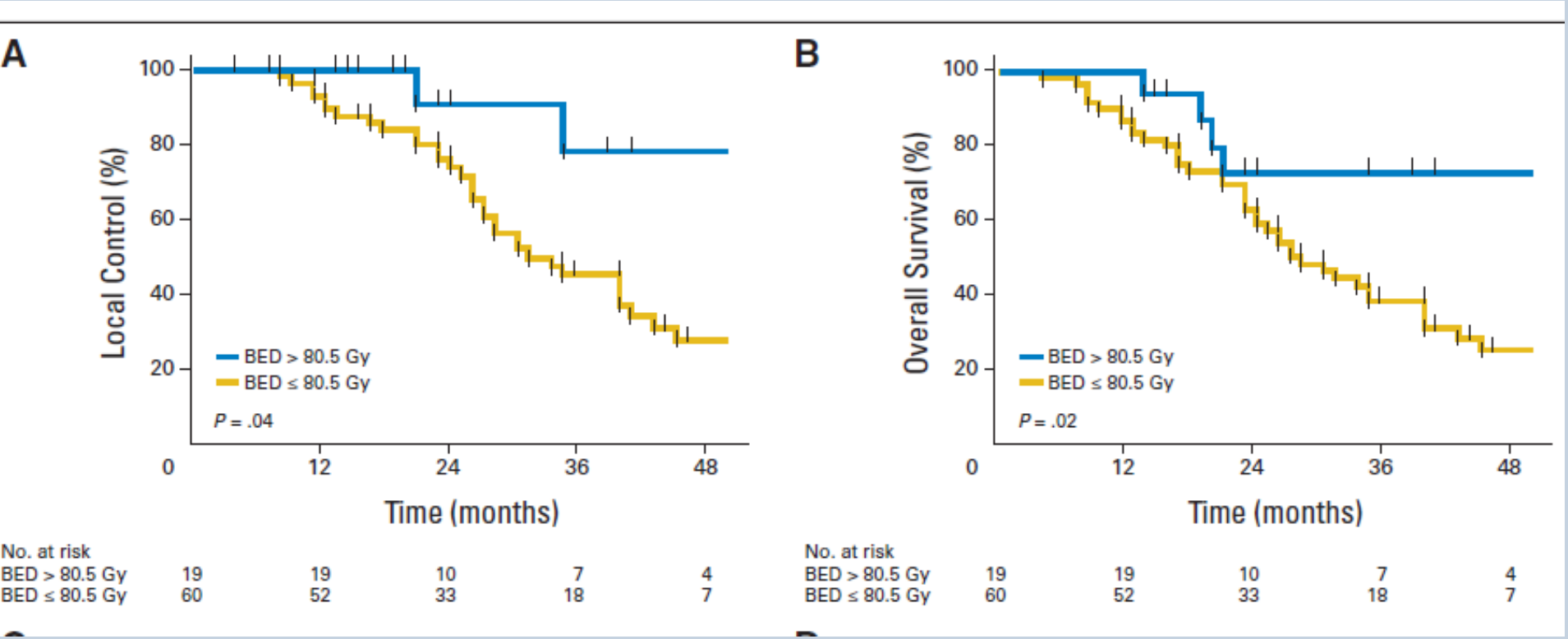
Reference	Pt(n)	Total Dose (Gy)	#	12-mth LC (%)	Median OS (mths)	Comments
Herfarth 2001	3	14 - 26	1	71	NR	Target volume covered by 80% isodose
Tse 2008	10	32.5	6	65	15	Hypofractionated stereotactic RT
Goodman 2010	5	18 - 30	1	77	29	Single-fraction dose escalation study
Kopek 2010	27	45	3	NR	11	22% rate of serious GI injury
Polistina 2011	10	30	3	NR	36	All pts received concurrent Gem
Barney 2012	10	55	5	100	14	Includes both recurrent and metastatic lesions
Ibara 2012	11	30 (22-50)	1-10	50	11	Data from 4 academic centres in the US

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



Crane JCO 2015

Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With 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**.

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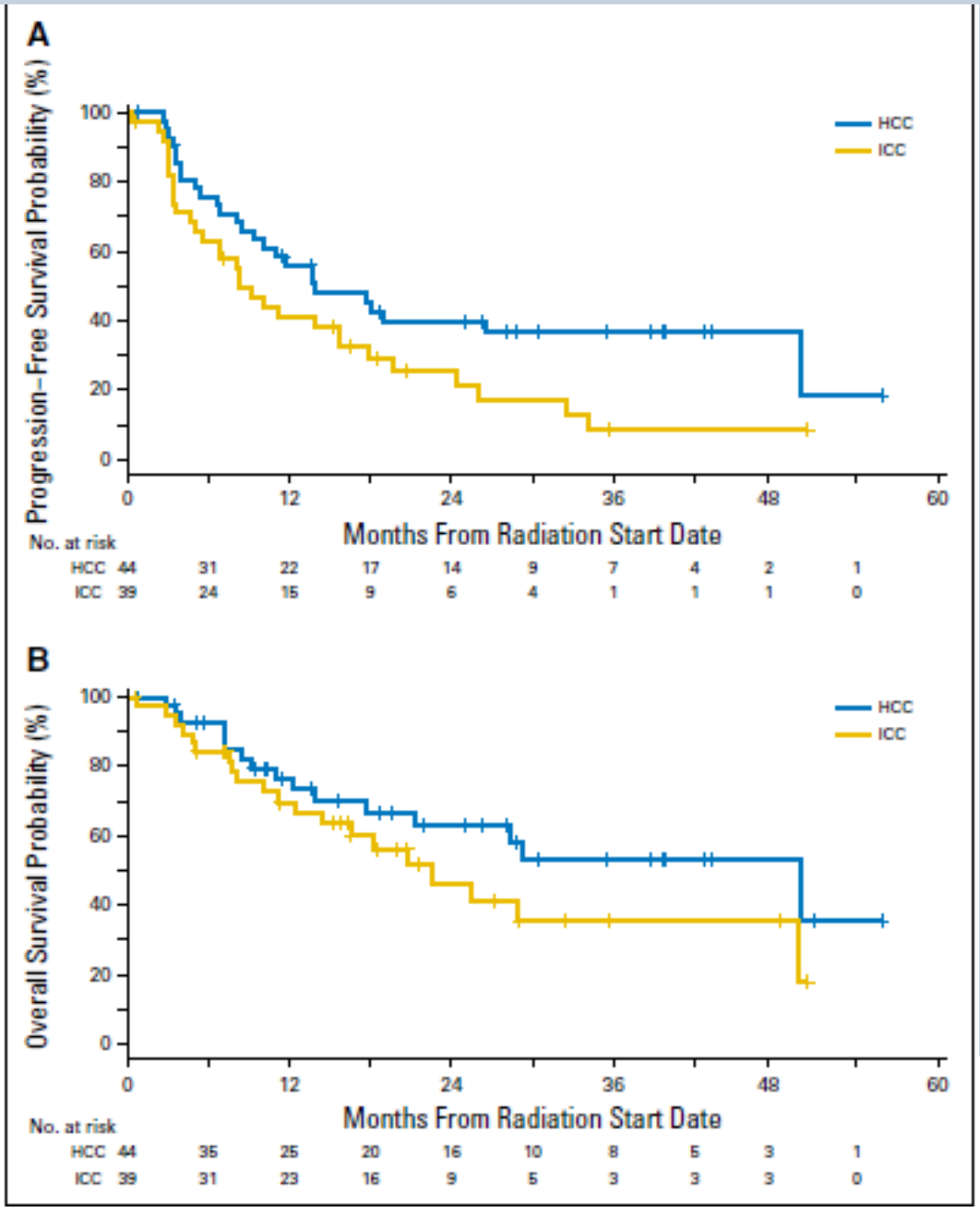
Hong JCO 2015



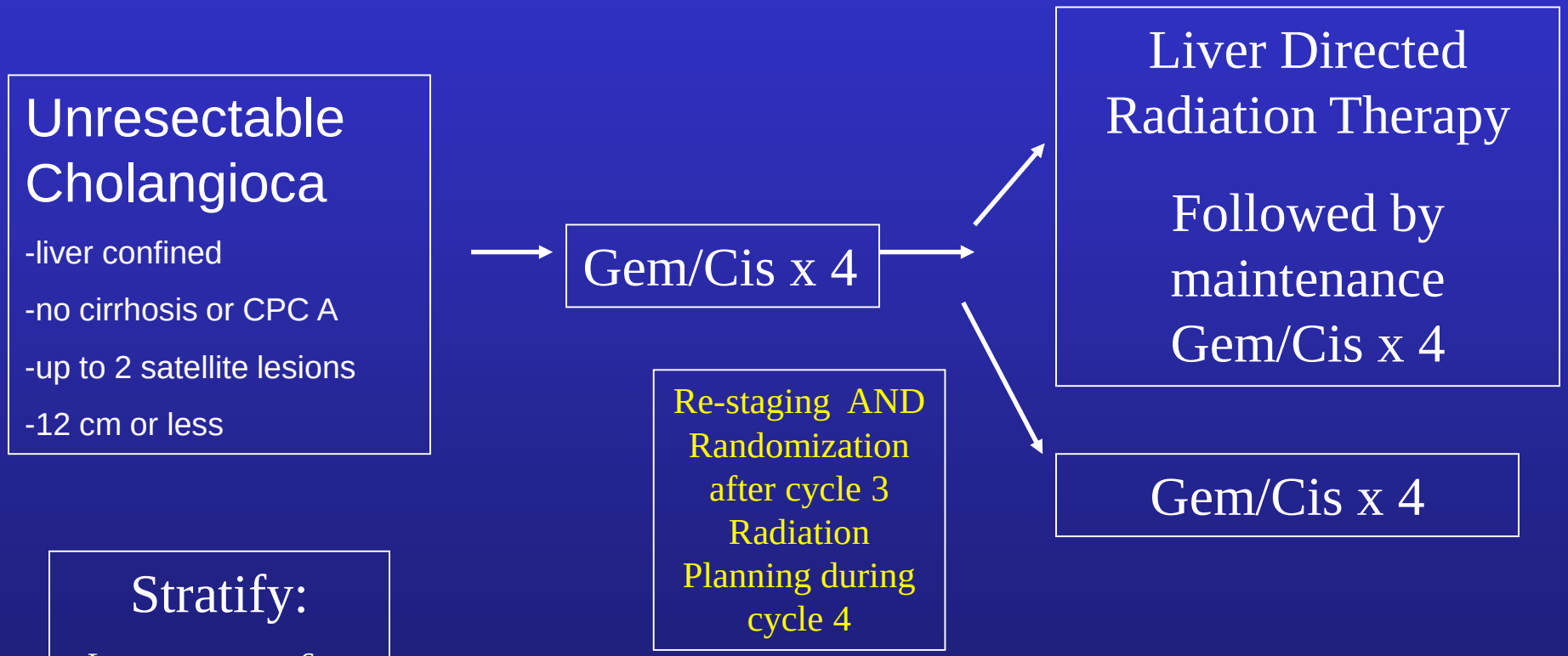
OS at 2 years

63.2% for HCC

46.5% ICC

Hong JCO 2015

US: RTOG 1320 – Phase III Trial



Hong, PI, Activated 2014

UK ABC 07 Addition of stereotactic body radiotherapy (SBRT) to systemic chemotherapy in locally advanced biliary tract cancer

If SBRT is added to chemotherapy in the treatment of locally advanced BTC then outcomes could be improved

Study design

randomised phase II study (with a feasibility run-in) with 2:1 randomisation between chemotherapy + SBRT and chemotherapy alone, respectively

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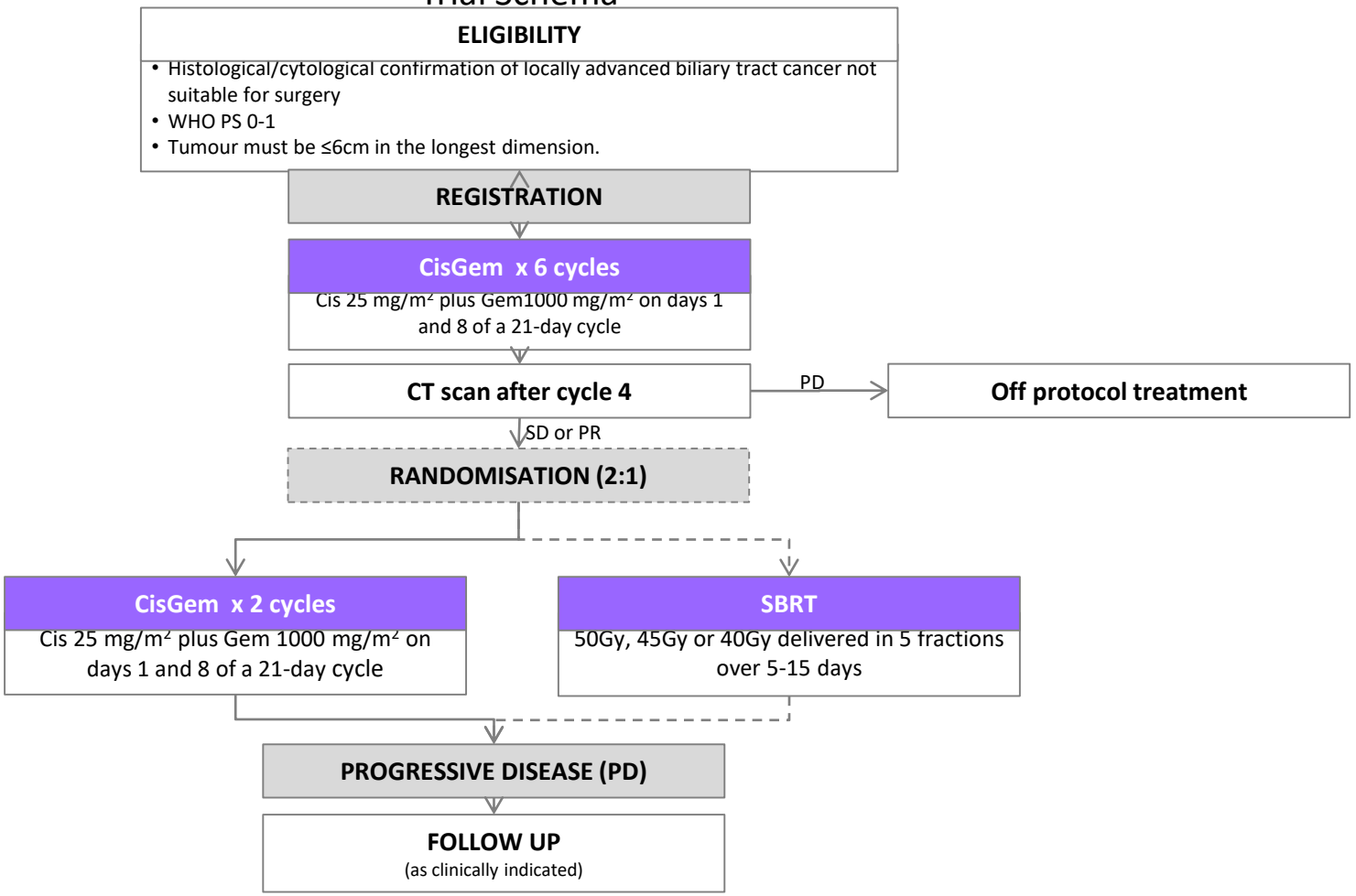
ABC07

Trial Schema

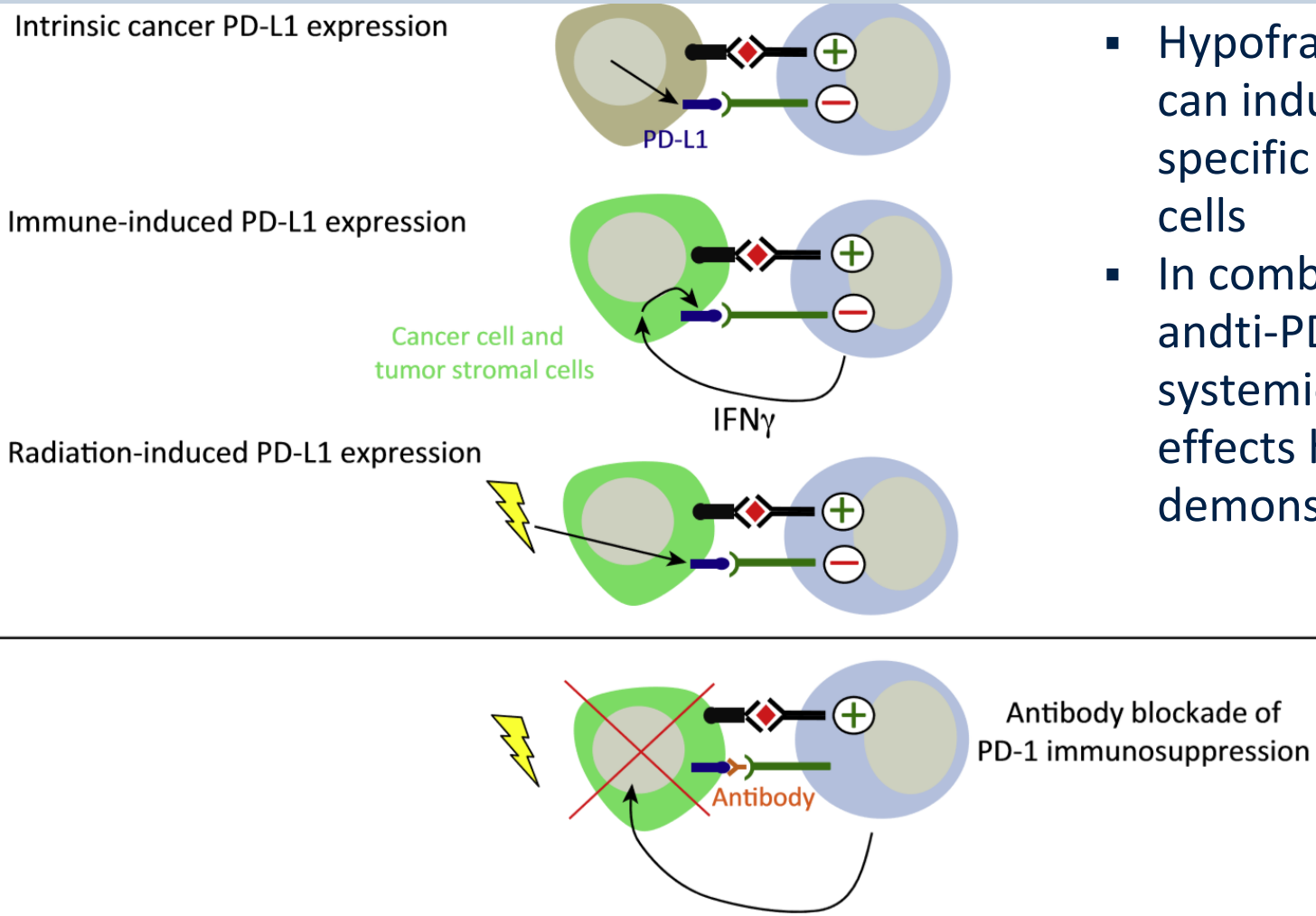


an improvement in the PFS from 45% to 62% at 12 months
This is equivalent to an extension of the median PFS from 10.4 to 17.4 months or a target HR 0.60.

Current status

- US and UK study harmonised endpoints
- US study suspended due to loss of equipoise
- UK study doing well- we have been successful in the feasibility phase
- We have applied for funding to CRUK to continue and complete the study

Can RT augument immune response?



- Hypofractionated RT can induce tumour specific cytotoxic T cells
- In combination with andti-PD1 local and systemic (abscopal) effects have been demonstrated

Final remarks

- Radiotherapy will have a role to play in the treatment of cholangiocarcinoma
- Supporting ABC07 study is key to establish a role for RT inoperable tumours
- Further research include considering, incorporating protons, and designing combination RT IO to enhance response in metastatic cancers
- We hope to test the role of local radiotherapy in the post-operative setting for patients that have positive margin after resection

Thank you

- Acknowledge funding form MRC grant MC_UU_00001/2
- CRUK (ref: C43735/A18752) to undertake ABC07 study
- ABC team