Multidiscipinary Interactive Session, ESMO Madrid, September 2014

Locally advanced pancreatic cancer – radiation oncology

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I have no conflicts of interest to report

Pancreatic cancer - presentation

- Non-metastatic
  - resectable
  - borderline resectable
  - non-resectable

  } LAPC
- Metastatic

Pancreatic cancer - presentation

- Non-metastatic
  - resectable 10-15%
  - borderline resectable
  - non-resectable

  } LAPC 30-35%
- Metastatic 50%

Pancreatic cancer - presentation

- Non-metastatic
  - resectable 10-15%
  - borderline resectable
  - non-resectable

  } LAPC 30-35%
- Metastatic 50%

- The non-metastatic will soon become metastatic in most patients

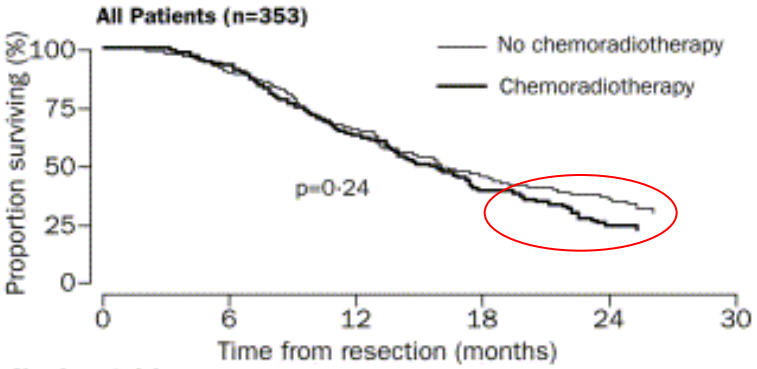
Locally advanced pancreatic cancer

- Is a systemic disease
- The clinical problem is a lack of effective systemic therapies
- What can radiation contribute with?

Locally advanced pancreatic cancer

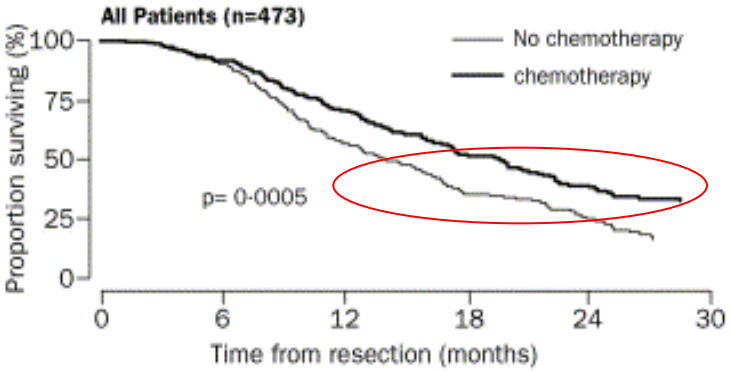
- Is a systemic disease
- The clinical problem is a lack of effective systemic therapies
- What can radiation contribute with?
  - No evidence of positive effects from RCTs
    - ESPAC-1 and others as adjuvant
    - LAP-07 in LAPC
  - Multiple phase II trials give some hints

ESPAC -1, negative for CRT, positive for CT adjuvant



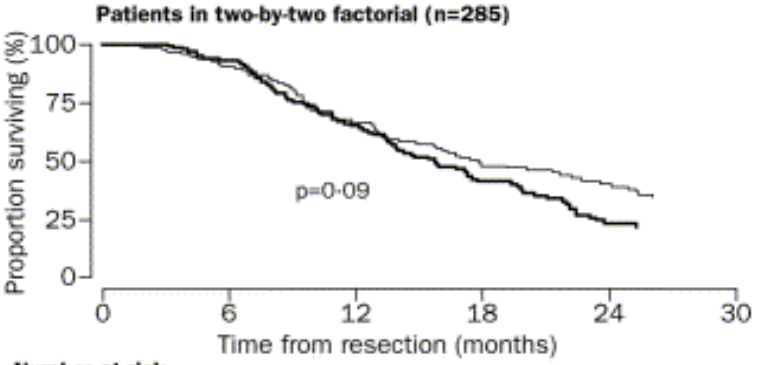
Number at risk

No chemoradiotherapy	178	136	92	54	38
Chemoradiotherapy	175	139	83	43	23



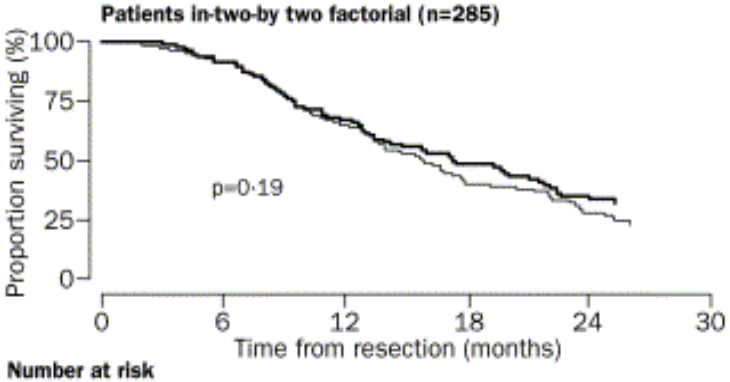
Number at risk

No chemotherapy	235	176	98	53	33
Chemotherapy	238	179	123	81	64



Number at risk

No chemoradiotherapy	143	110	76	46	34
Chemoradiotherapy	142	112	69	35	18



Number at risk

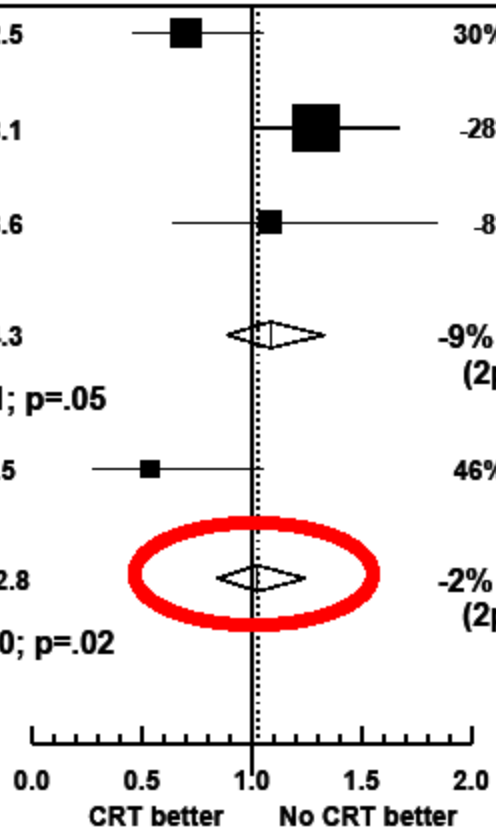
No chemotherapy	139	108	68	36	23
Chemotherapy	146	113	76	47	29

(Neoptolemos et al, Lancet 2001;358:1576-85)

Meta-Analysis of Adjuvant Treatment: Chemoradiotherapy

	Events/Patients CRT	Events/Patients No CRT	CRT events (O-E)	CRT events Var.	Reduction (% & SD)
EORTC	44/63 (69.8%)	48/57 (84.2%)	-8.1	22.5	30% sd 18
ESPAC1-2x2	125/145 (86.2%)	112/144 (77.8%)	14.8	58.1	-28% sd 15
ESPAC1-plus	27/33 (81.8%)	29/36 (80.6%)	1.1	13.6	-8% sd 28
Subtotal:	196/241 (81.3%)	189/237 (79.7%)	7.7	94.3	-9% sd 11 (2p=.43)
Heterogeneity between 3 groups $\chi^2_2 = 6.1$; p=.05					
GITSG*	15/21 (71.4%)	19/22 (86.4%)	-5.3	8.5	46% sd 26
Subtotal:	211/262 (80.5%)	208/259 (80.3%)	2.5	102.8	-2% sd 10 (2p=.81)
Heterogeneity between 4 groups $\chi^2_3 = 10.0$; p=.02					

Hazard Ratio & CI CRT:No CRT

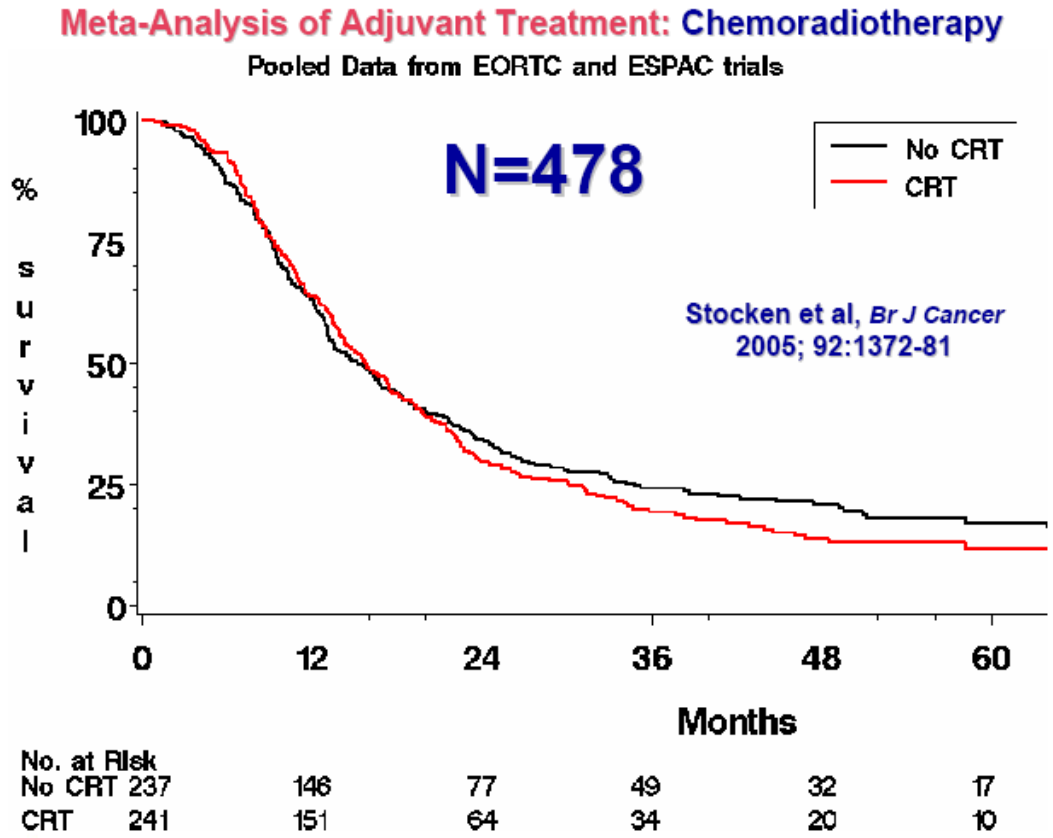


95% or 95% confidence intervals

* IPD not available

Stocken et al, *Br J Cancer* 2005; 92:1372-81

Adjuvant CRT does not work



Why not?
Pancreas cancer is a systemic disease
No QC of the RT in ESPAC-1
Low RT-dose, split course (shouldn´t work with present knowledge, historical interest)
Basically we don´t know if CRT works adjuvant, a trial ongoing

RTOG 0848

actively recruiting again testing ± CRT adjuvant (with QA of the RT)

FIRST RANDOMIZATON

STRATIFY

Nodal Status:
1: involved
2: uninvolved

CA19-9 result:
1: ≤ 90
2: > 90 – 180

Surgical margins:
1: positive (R1)
2: negative (R0)

RANDOMIZE

Arm 1:
Gemcitabine x 5 cycles

Arm 2:
Gemcitabine + Erlotinib x 5 cycles

Evaluate to Confirm No Progression

If no progression, then:

STRATIFY

1. Arm 1: gemcitabine
2. Arm 2: gemcitabine + erlotinib

SECOND RANDOMIZATON
For Non-Progressing Patients

RANDOMIZE

Arm 3:
1 cycle of chemotherapy

Arm 4:
1 cycle of chemotherapy followed by RT with either capecitabine or 5-FU

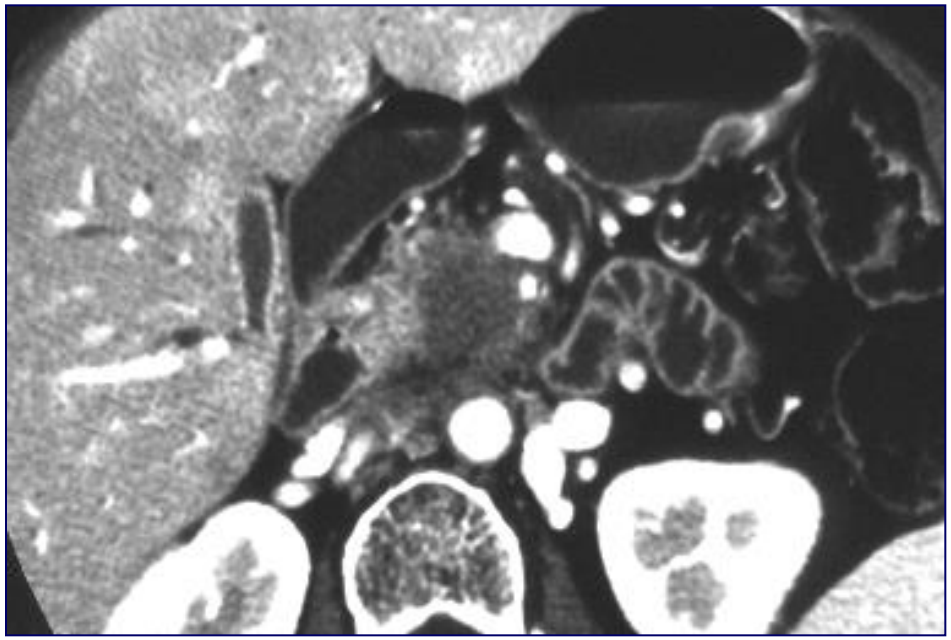
Is based upon RTOG 9704, no diff CRT with gem or 5-FU, diff according to RT quality (Regine Ann Surg Oncol 2011; Abrams Red J 2012)

LAP 07

Gercor-FFCD, international groups

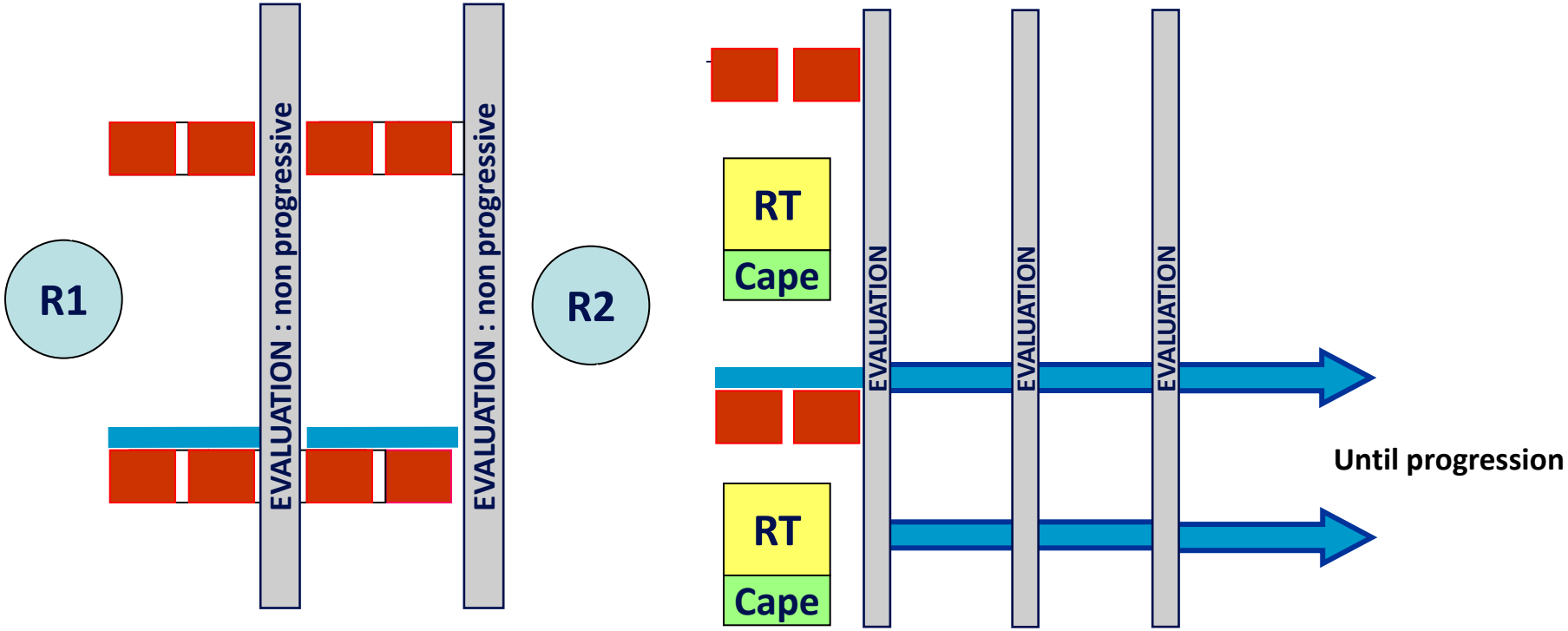
Locally Advanced Pancreatic adenocarcinoma

PI Pascal Hammel, Clichy, France



Bengt Glimelius, co-ordinator Sweden

Design of LAP07 study



Gemcitabine 1000 mg/m²/wk x 3

Erlotinib 100 mg/d

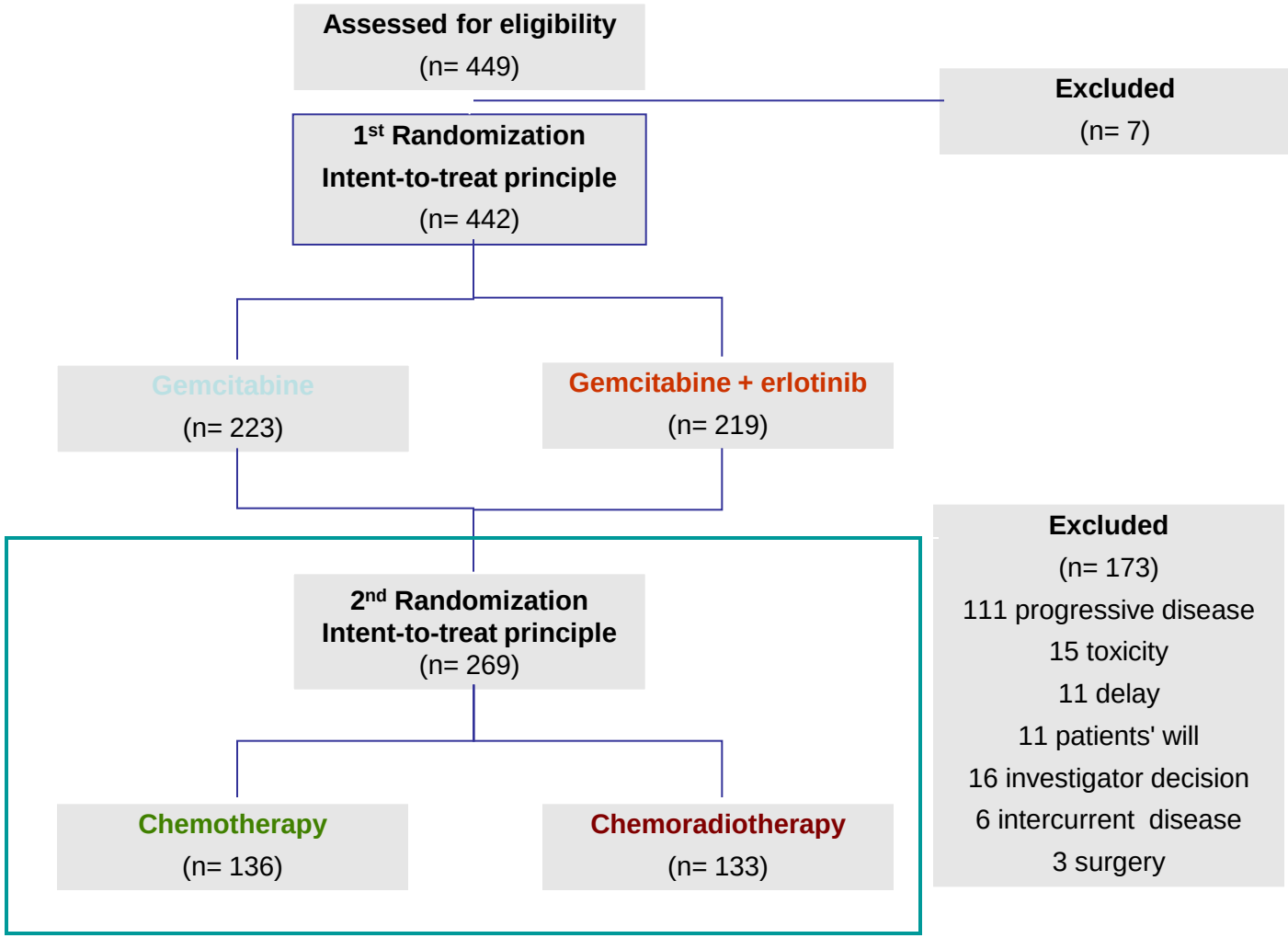
Erlotinib 150 mg/d as single agent (maintenance)

RT
Cape

Radiation therapy 54 Gy (5 x 1.8 Gy/d) with concurrent Capecitabine 1600 mg/m²/d

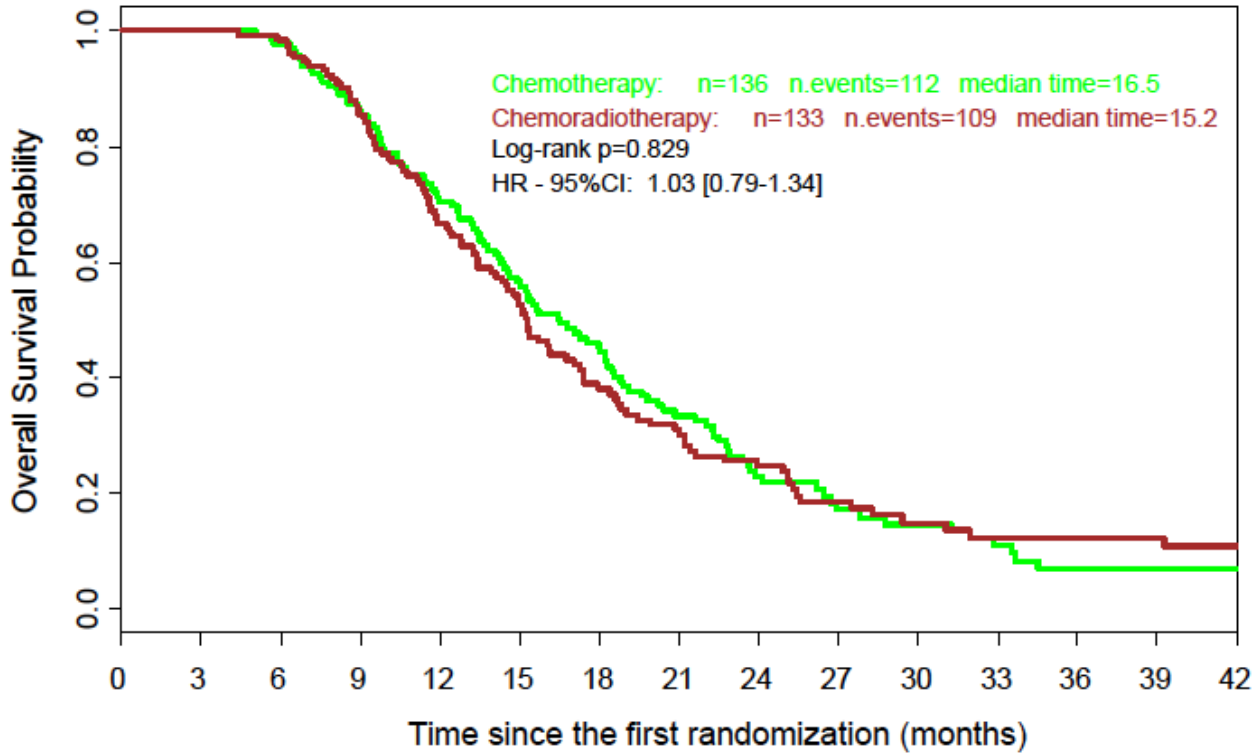
erlotinib did not add efficacy in LAPC

Flow Chart



Hammel P et al. ASCO 2013, Huguet F et al, ASCO 2014

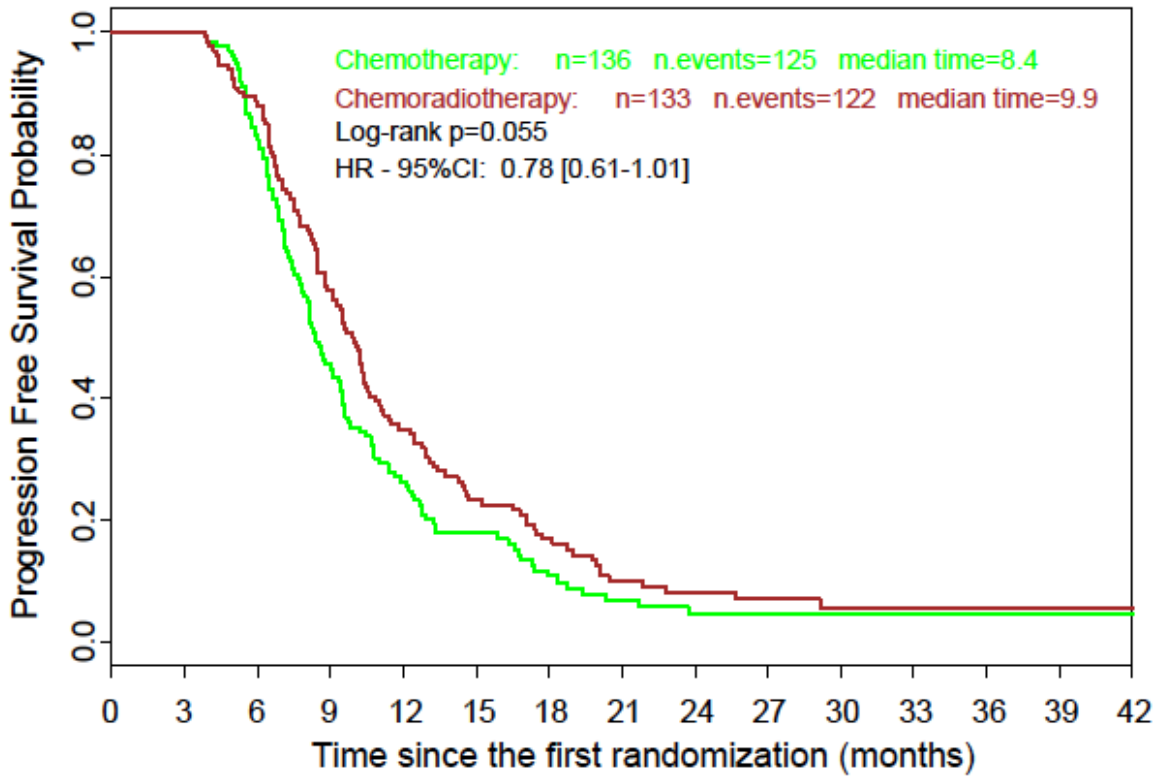
LAP-07, overall survival



N at risk

Chemotherapy	136	136	133	117	94	70	55	39	24	14	12	8	4	4	4
Chemoradiotherapy	133	133	131	113	87	66	45	34	26	18	12	9	9	8	6

LAP-07, PFS



N at risk

Chemotherapy	136	136	113	61	35	21	12	7	3	1	1	1	1	1	1
Chemoradiotherapy	133	133	117	76	45	30	21	11	8	7	4	4	4	4	4

Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study

Huguet F, Hammel P, Vernerey D, Goldstein D, Van Laethem JL, Glimelius B, Spry N, Paget-Bailly S, Bonnetain F, Louvet C

France, Belgium, Australia, New Zealand, Sweden

AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

BGDO Belgian Group of Digestive Oncology

GERCOR

PRODIGE PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

NORDIC GROUP

ASCO 2014

Site of first progression

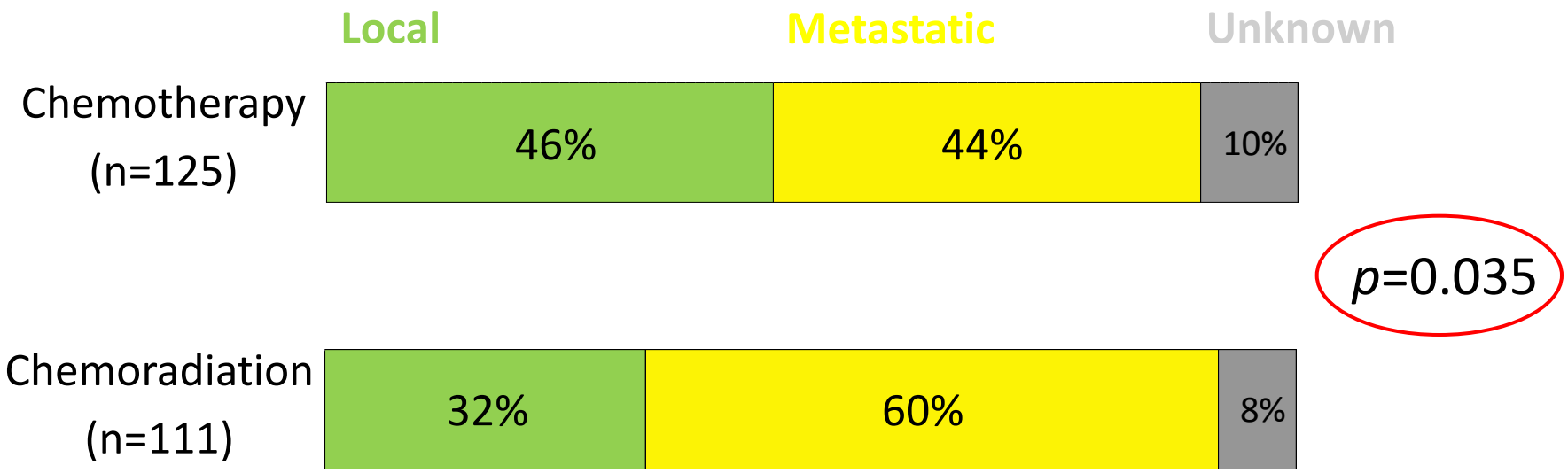
- **R2 patients**:

  236/269 patients (88%) with tumor progression

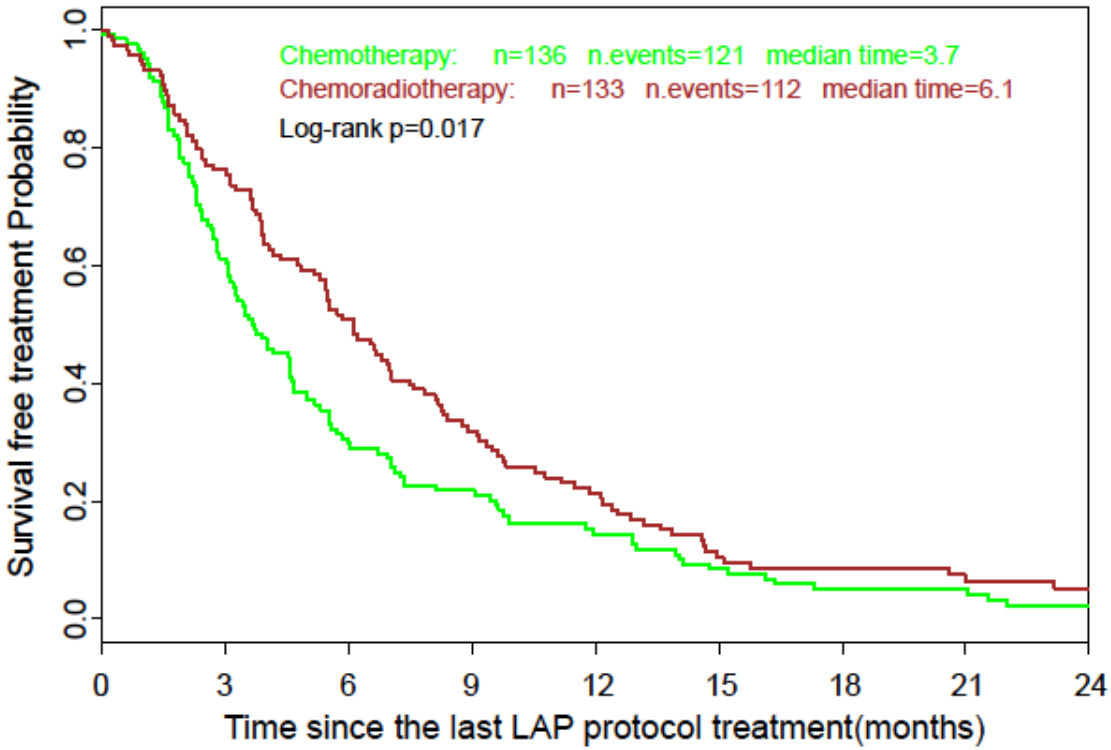
  93 with local progression only (39%)

  122 with metastatic (± local) progression (52%)

  21 unknown (9%)



LAP-07, time to new txt



N at risk

Chemotherapy	136	75	37	27	17	10	6	6	2
Chemoradiotherapy	133	89	60	37	24	11	8	6	5

Time without treatment

- 24 patients (19%) in the CT arm and 30 patients (27%) in the CRT arm did not receive a second line of treatment (p=0.1)

- **In patients who received a second line of chemotherapy:**

Median time before reintroduction of chemotherapy

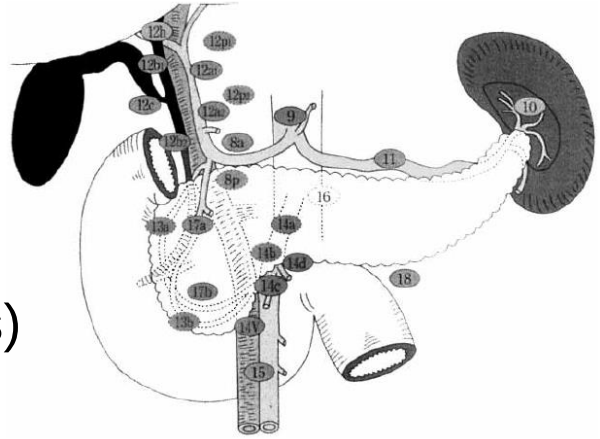
Chemotherapy (n= 101)	**Chemoradiation** (n= 81)
3.2 months	5.2 months
(0.3-22)	(0.2-25.7)

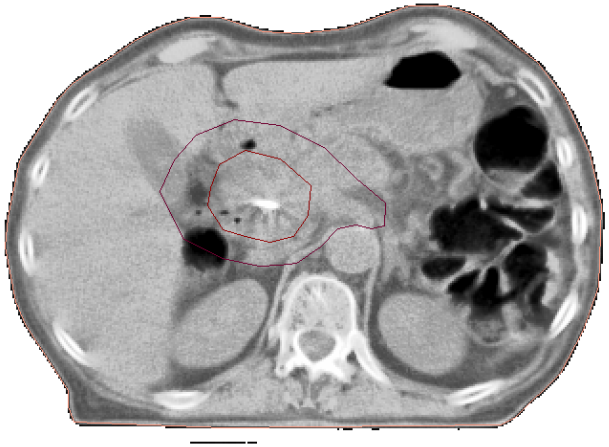
p=0.045

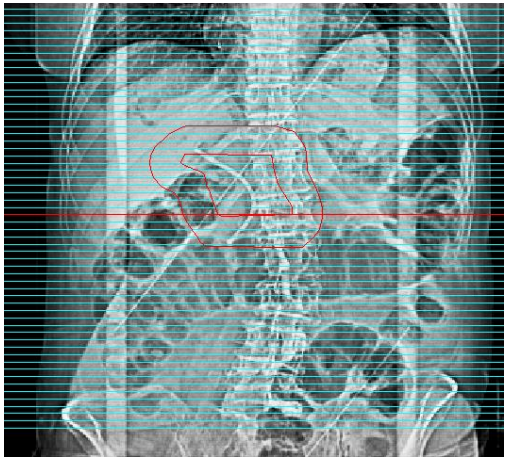
Presented by: F. Huguet

Radiation modifies the clincial course
Why doesn´t it work better?

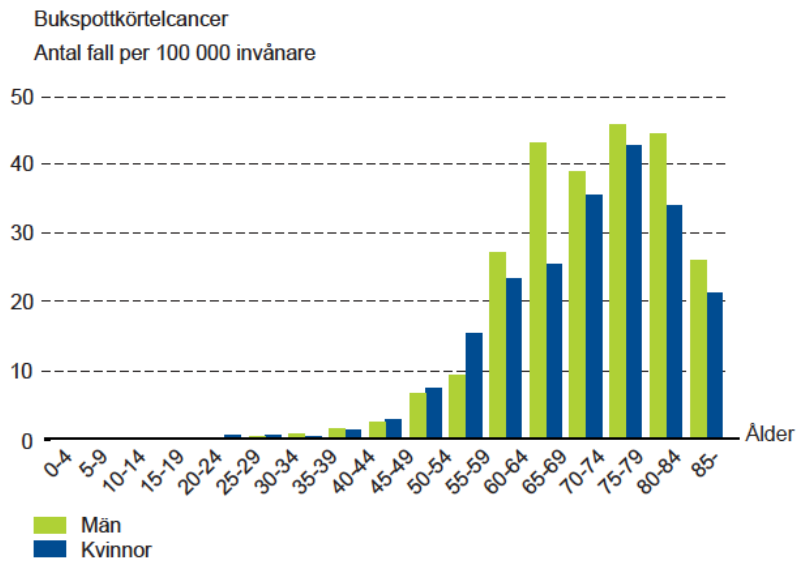
Lgll mets frequent
For cure, large volumes needed
Standard dose about 50 Gy with fluoropyrimidine/gemcitabine insufficient for macroscopic tumour (most solid cancers)
The RT given in the past ”ineffective”





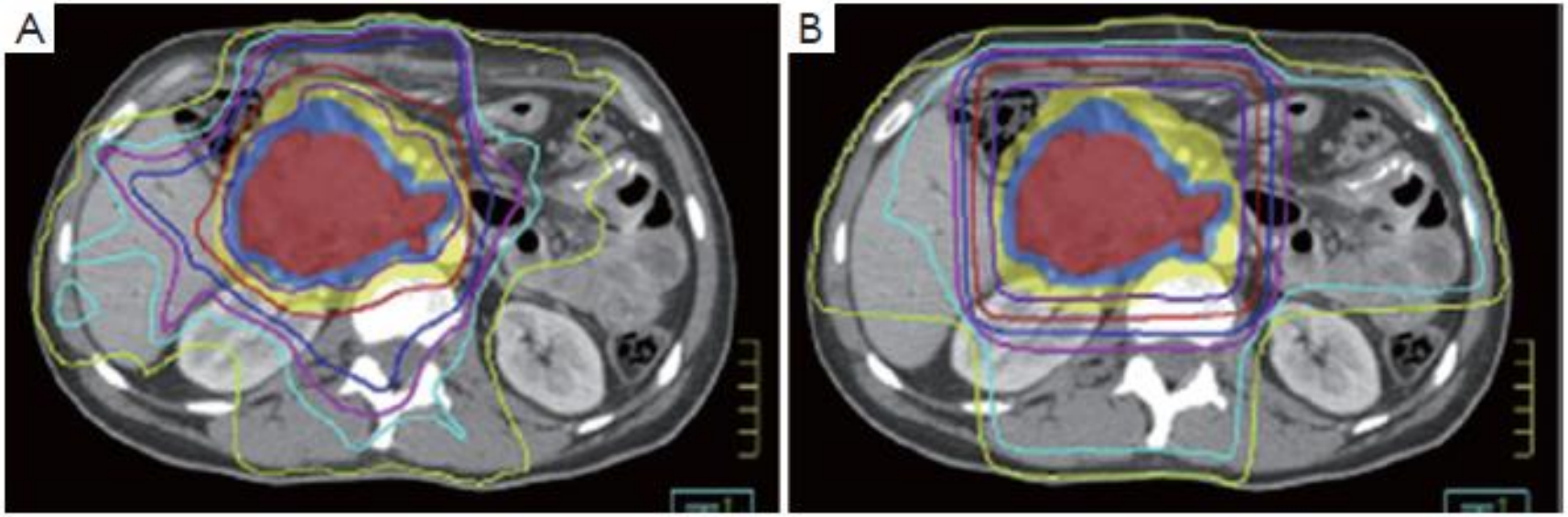


Pankreas cancer patients are elderly



- Do not tolerate extensive CRT very well
- CRT quite toxic also for younger
- Better techniques are available
  - could decrease toxicity/allow dose escalation

Better techniques are available



VMAT/IMRT is just one step vs 3D-CRT,
IMPT would likely do it even better, SBRT

Radiation for LAPC

- Not very effective as given
- Has palliative effects
- Not worse than chemotherapy
- The large trials not done (as usual for RT)
- Could be done better
  - both better trials and
  - with better techniques/QA and QC
  - worthwhile explore in new trials (many ongoing)
    - –but seldom part of routine (except for palliation)