

Adjuvant Therapy in Pancreas Ca

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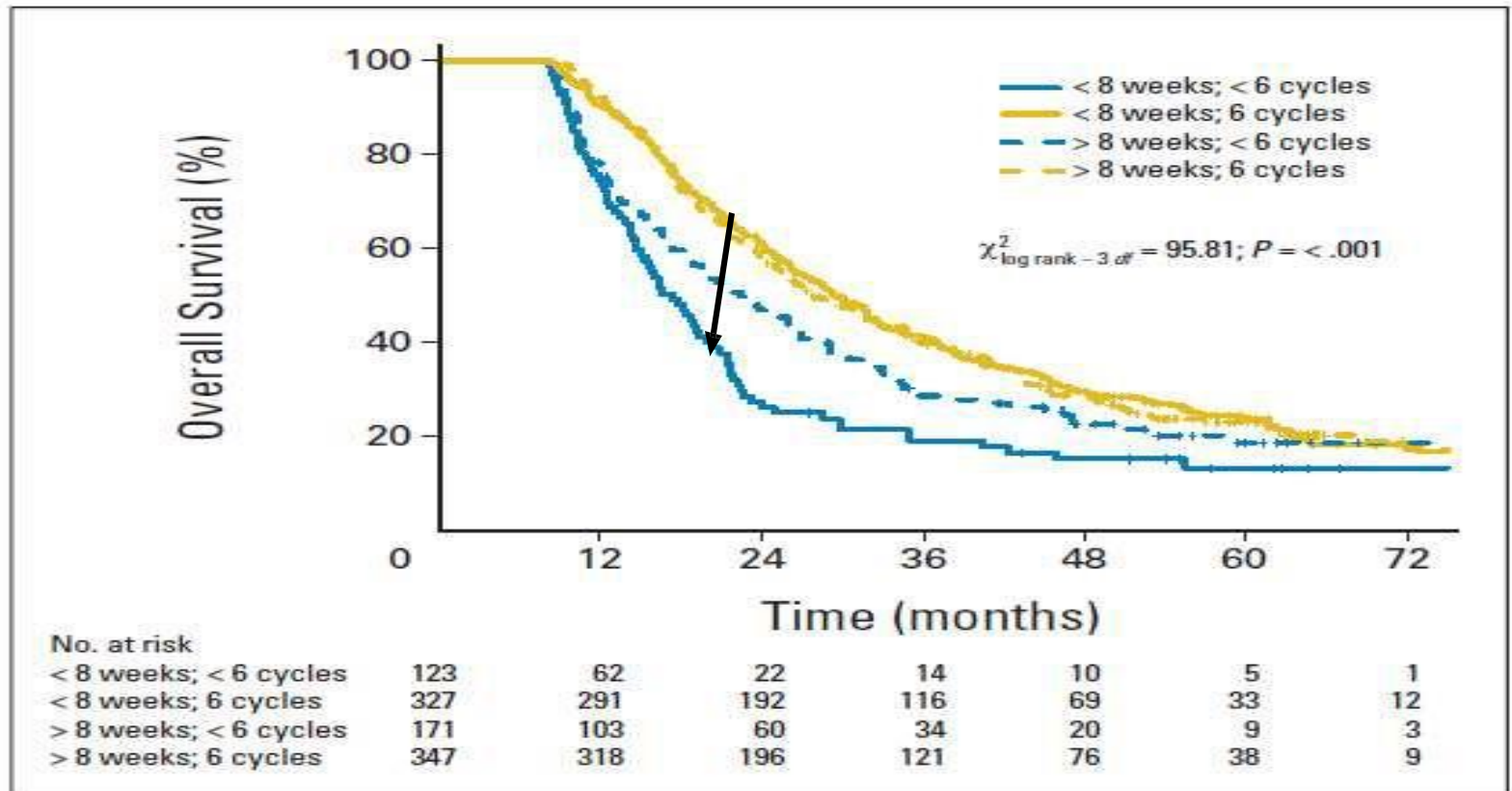
Gibbs Cancer Center
& Research Institute

Pancreatic Adenocarcinoma

- Pancreatic ductal adenocarcinoma (PDAC) is now the third leading case of cancer deaths in the USA
- Although there have been recent advancements in systemic therapy for metastatic disease with the FOLFIRINOX and gemcitabine/nab-paclitaxel regimens, the survival rates for PDAC remain poor
- The most established risk factor pancreas cancer is cigarette smoking and is associated with about 25% of the cases.
- A minority of PDAC patients (less than 20%) are diagnosed at an early stage where surgery may be beneficial
 - In these patients, accurate staging is required to define potential resectability
- In patients with resectable PDAC, the current standard of care is upfront surgery followed by adjuvant therapy

1. American Cancer Society 2016. Cancer Facts and Figures
2. Fuchs CS et al. Arch Intern Med. 1996 Oct;156(19):2255-60.

Start of adjuvant CT



ESPAC trial retrospective analysis:

- Up to **12 weeks start after surgery** does not affect prognosis
- Completing 6 cycles of chemotherapy impacts survival

Pancreatic Adenocarcinoma: Definition of Resectability

| | Potentially Resectable | Borderline Resectable | Unresectable |
|--------------|------------------------|---|-----------------------------|
| SMV-PV | T-V-I < 180° | T-V-I ≥ 180° and / or reconstructable occlusion | Unreconstructable Occlusion |
| SMA | No T-V-I | T-V-I < 180° | T-V-I ≥ 180° |
| CHA | No T-V-I | Reconstructable short-segment T-V-I of any degree | Unreconstructable |
| Celiac Trunk | No T-V-I | T-V-I < 180° | T-V-I ≥ 180 |

Abbreviations: SMV-PV, superior-mesenteric vein-portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery; T-V-I, tumor-vessel interface

Adjuvant Therapy Beneficial?

**5-FU + radiotherapy (RT) with systemic 5-FU for one year
Vs.
No additional treatment**

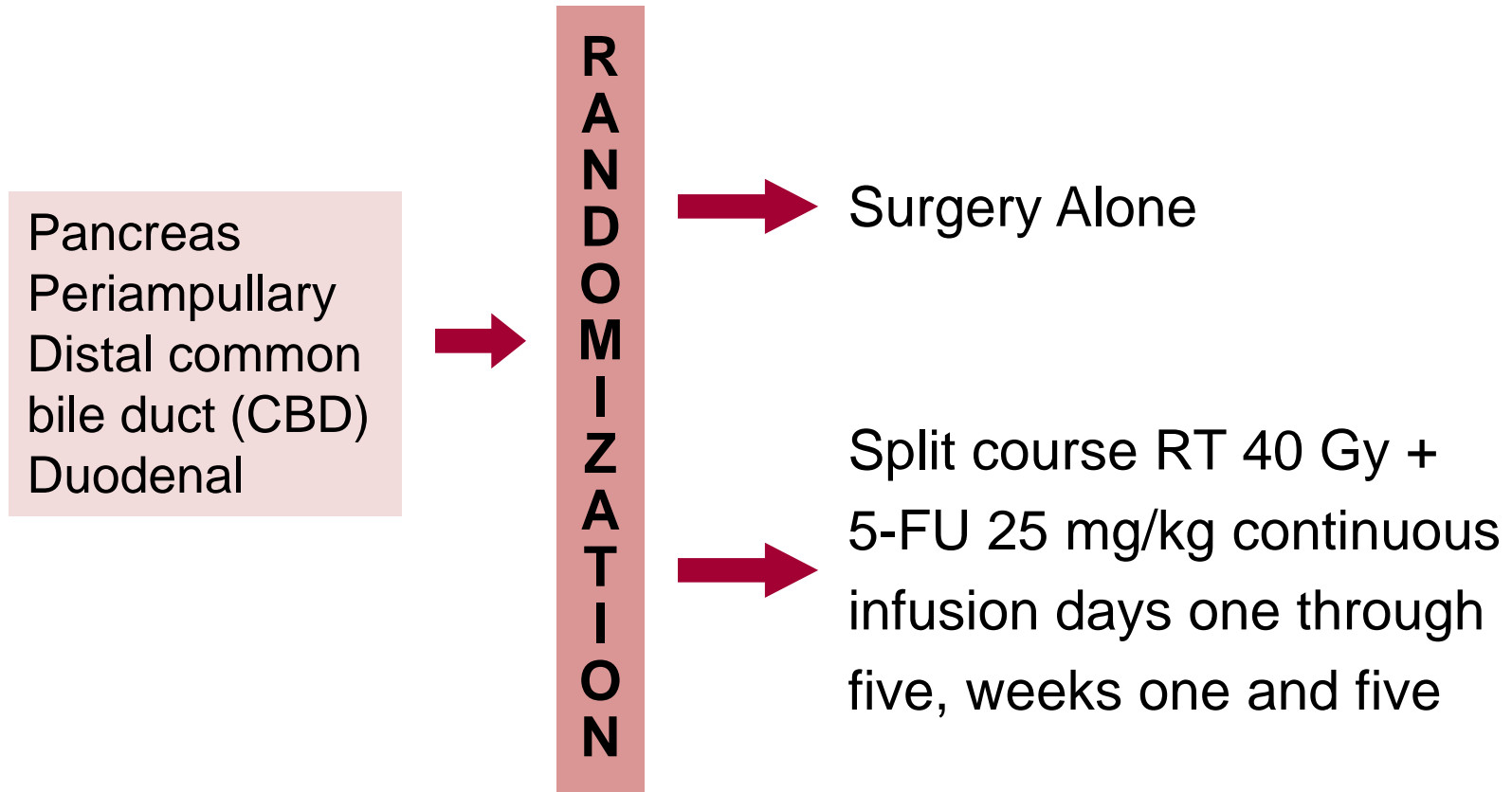
Gastrointestinal Tumor Study Group (GITSG) [N = 43]

- Median survival: 20 months vs. 11 months
- 5-year survival: 18% vs. 8%

But...

✓ 43 patients in eight years!

EORTC: Adjuvant Chemoradiotherapy



EORTC: Adjuvant Chemoradiotherapy

| | Treatment N = 110 | Observation N = 108 | <i>P</i> Value |
|---------------------------------|----------------------|------------------------|----------------|
| Median survival | 24.5 months | 19 months | .208 |
| Two year survival | 51% | 41% | |
| Progression-free survival (PFS) | 17.4 months | 16 months | .643 |
| Two year PFS | 37% | 38% | |
| Progression of disease (POD) | 65% | 66% | |

EORTC: Adjuvant Chemoradiotherapy

| | Treatment | Observation | <i>P</i> Value |
|---|------------------------------|------------------------------|----------------|
| Pancreas Median survival Two year survival | N = 60 17.1 months 34% | N = 54 12.6 months 26% | .099 |
| Periampullary Median survival Two year survival | N = 44 39.5 months 67% | N = 49 40.1 months 63% | .737 |

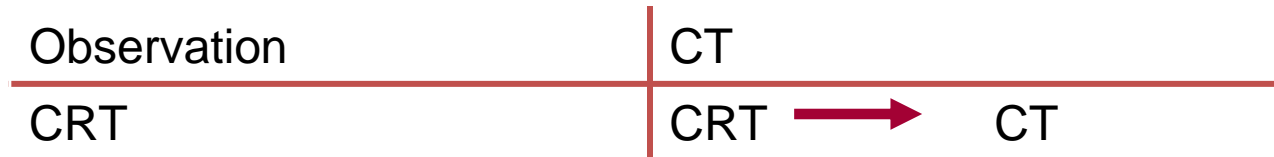
ESPAC-1: Trial Design

Adenocarcinoma pancreatic cancer
undergoing 'curative' resection

Randomize

(stratified by center, tumor type, resection margins)

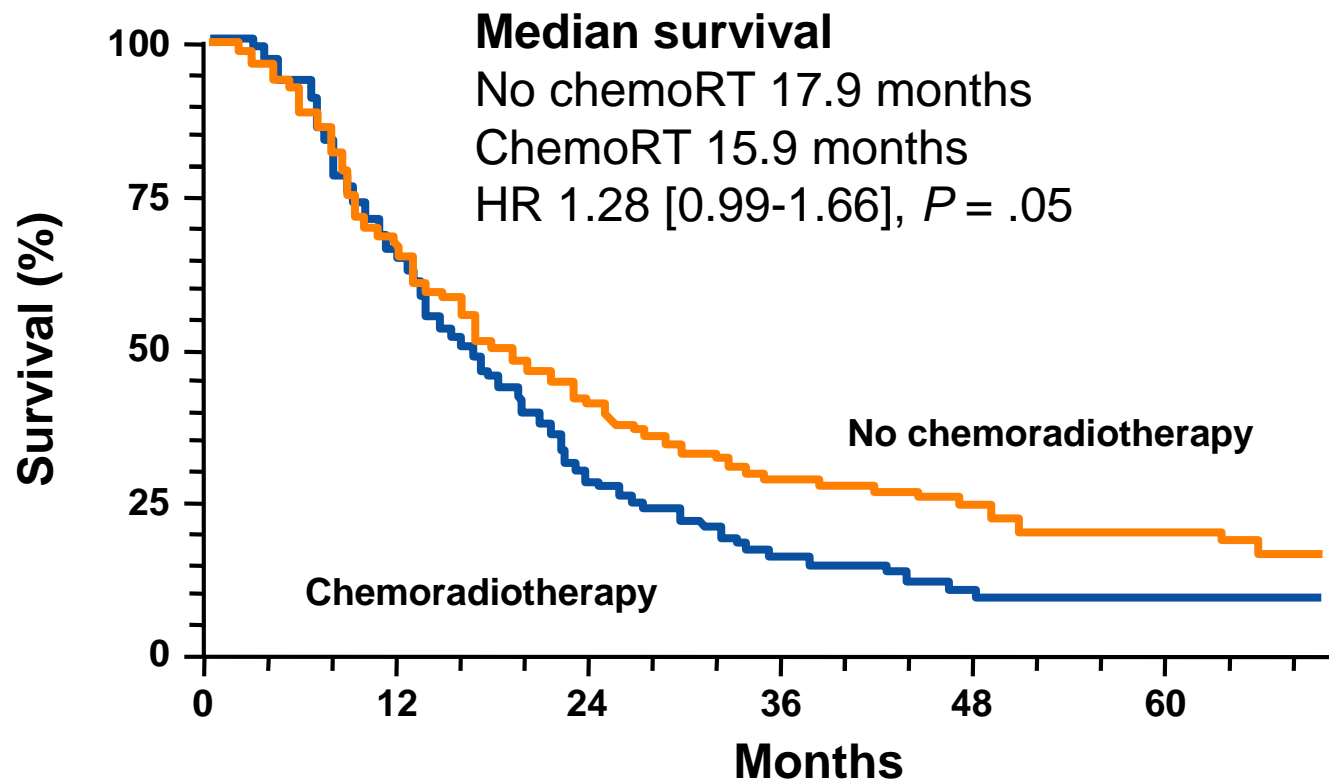
2 x 2 Factorial Design (Target 280)



Chemotherapy: 5-FU/LV [Mayo] x 6

Chemoradiation: 4000/20 [split] + bolus 5-FU.

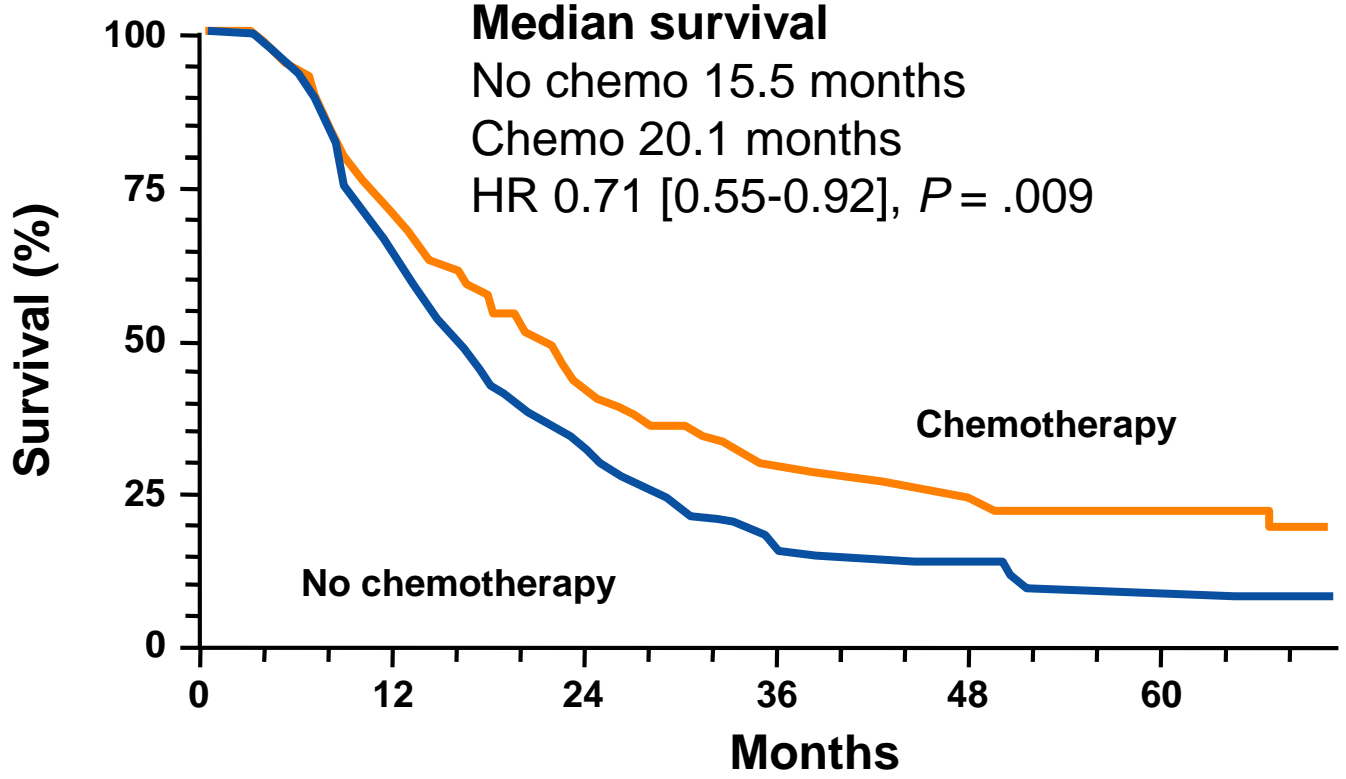
Survival by Adjuvant Chemoradiotherapy



No. at Risk

| | | | | | | |
|----------------------|-----|----|----|----|----|----|
| No chemoradiotherapy | 144 | 94 | 57 | 36 | 22 | 13 |
| Chemoradiotherapy | 145 | 94 | 40 | 20 | 11 | 5 |

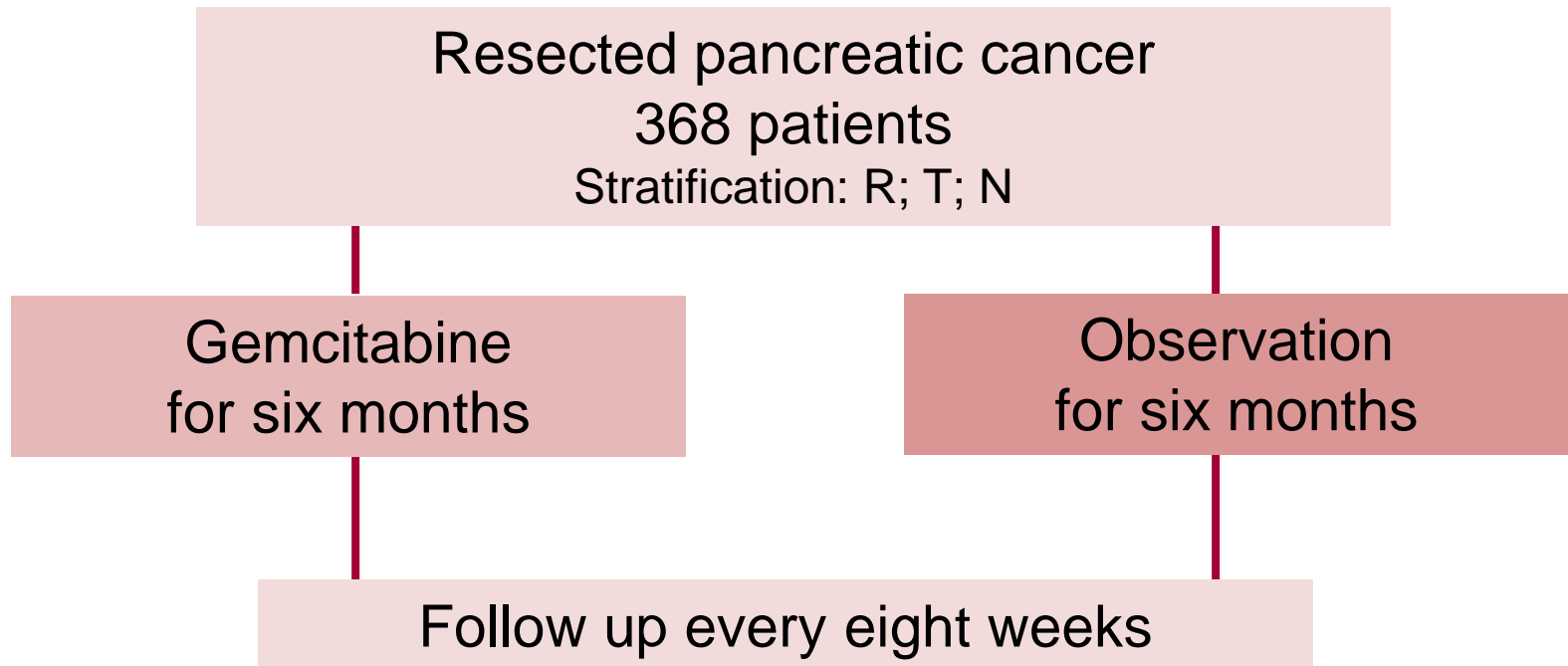
Survival by Adjuvant Chemotherapy



| No. at Risk | | | | | | |
|-----------------|-----|----|----|----|----|----|
| No chemotherapy | 142 | 89 | 41 | 18 | 11 | 7 |
| Chemotherapy | 147 | 99 | 56 | 38 | 22 | 11 |

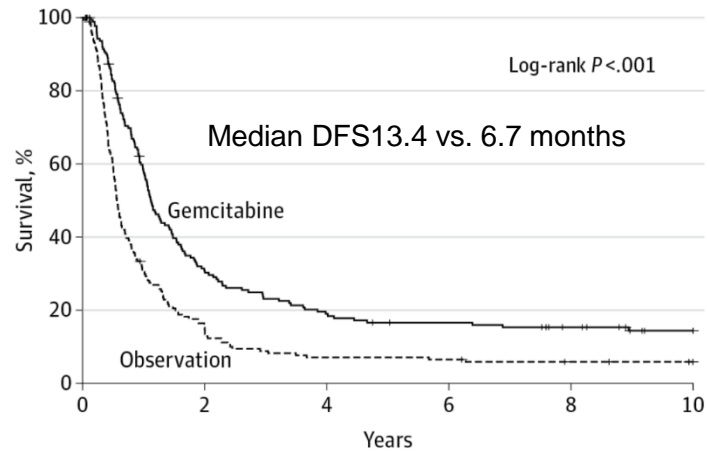
Neoptolemos JP et al. N Engl J Med. 2004 Mar;350(12):1200-10.

CONKO-001



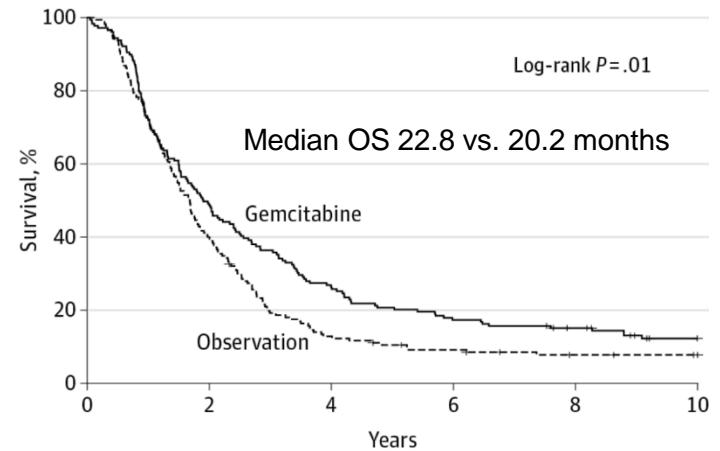
CONKO-001 Survival Results

A Disease-free survival



| No. at risk | | 0 | 2 | 4 | 6 | 8 | 10 |
|-------------|-----|----|----|----|----|----|----|
| Gemcitabine | 179 | 52 | 32 | 26 | 20 | 12 | |
| Observation | 175 | 26 | 12 | 11 | 8 | 6 | |

B Overall survival

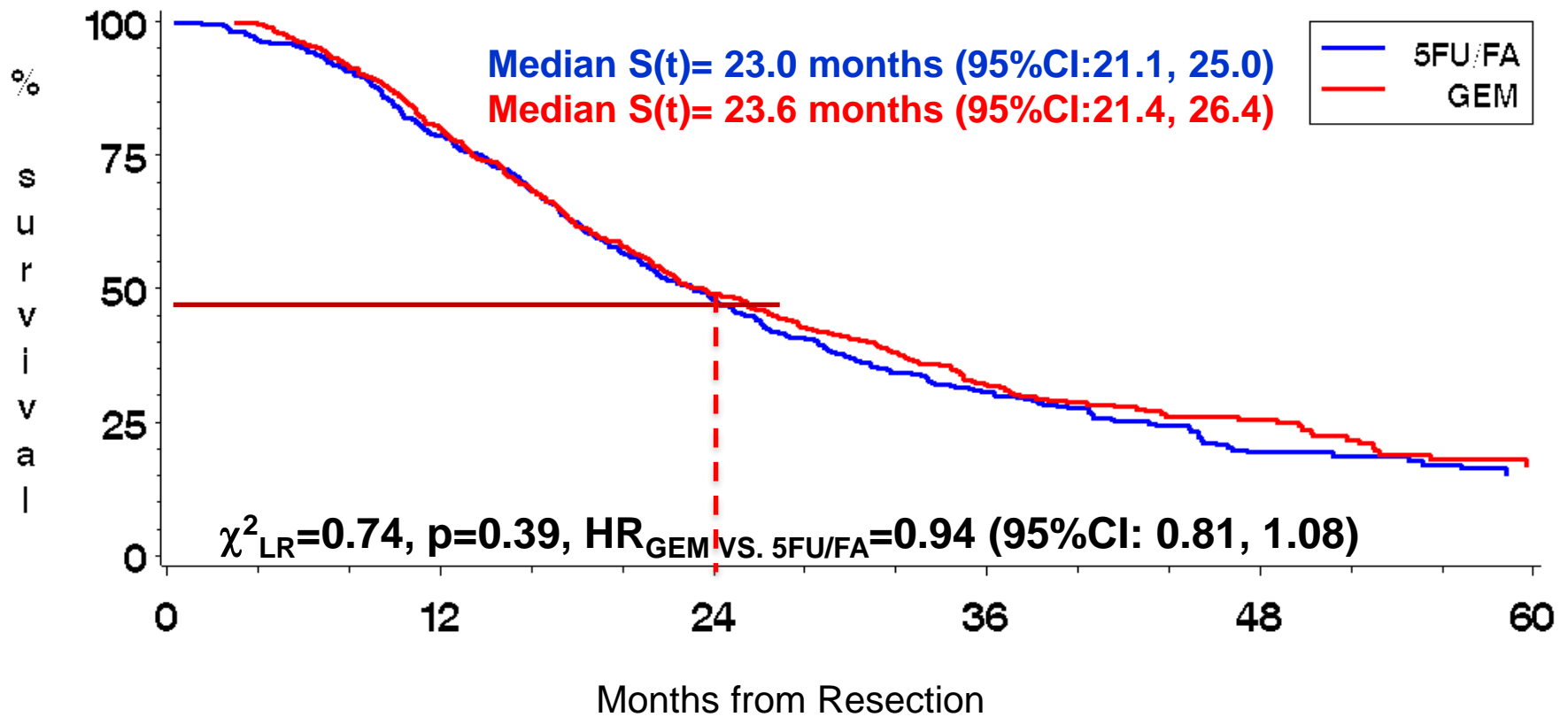


| No. at risk | | 0 | 2 | 4 | 6 | 8 | 10 |
|-------------|-----|----|----|----|----|----|----|
| Gemcitabine | 179 | 87 | 47 | 31 | 24 | 14 | |
| Observation | 175 | 70 | 22 | 14 | 9 | 7 | |

Oettle H et al. JAMA. 2007;297(3):311-313.

Abbreviations: DFS, disease free survival; OS, overall survival

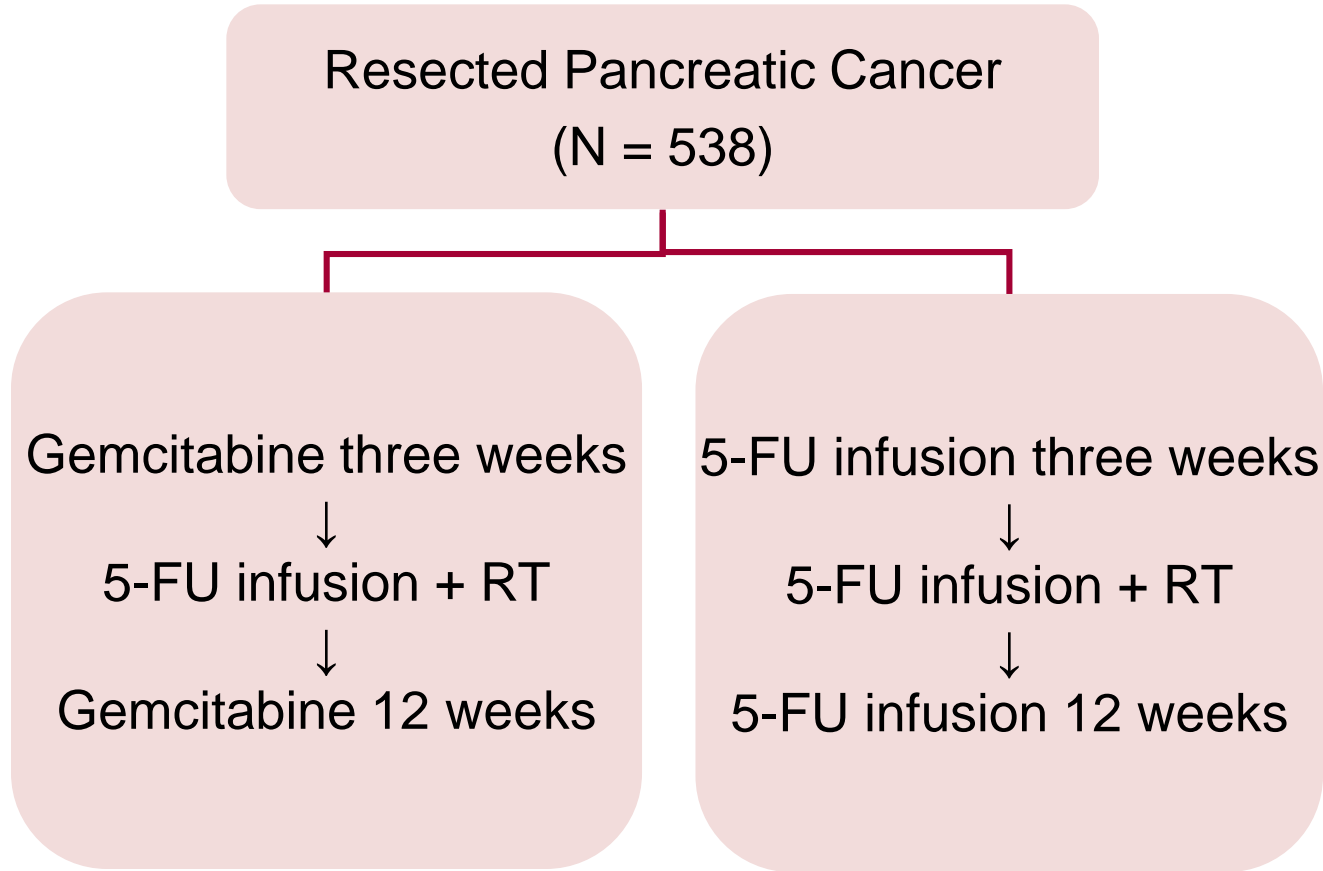
ESPAC-3, N=1,088: Gemcitabine Not Better Than 5-FU/FA



No. at Risk

| | | | | | | |
|--------|-----|-----|-----|-----|----|----|
| 5FU/FA | 551 | 413 | 249 | 109 | 36 | 15 |
| GEM | 537 | 415 | 251 | 103 | 42 | 13 |

US Intergroup Adjuvant (RTOG 97-04)



RTOG 97-04 Results

| Pancreatic Head (N = 380) | Gem Arm | 5-FU Arm |
|---------------------------|-------------|-------------|
| Median Survival | 20.5 months | 16.9 months |
| 3-Year Survival | 31% | 22% |

HR 0.79 (CI, 0.65- 1.03, $P = .09$)

No significant differences when body/tail tumors included
(N = 422, $P = .2$)

Summary of Adjuvant Trials Prior to 2016

| | GITSG | EORTC | ESPAC-1* | ESPAC-3 | CONKO-001 | RTOG 9704 |
|------------------------|-------------------------|-------------------|---------------------|------------------|---------------------|-------------------|
| Intervention | ChemoRT vs. observation | ChemoRT vs. Chemo | 5FU vs. observation | 5FU/FA vs. Gem | Gem vs. observation | Gem-RT vs. 5FU-RT |
| R1 resection | 0 | 19% [†] | 28% | 35% | 19% | 35% |
| T3 or T4 | NA | 0 | NA | 62% | 86% | 81% |
| Node-positive | 30% | 47% | 50% | 72% | 71% | 68% |
| Local recurrence | 47% | 51% [†] | 63% [‡] | NA | 37% | 23% |
| Median survival | 21 months | 17 months | 20 months | 23 months | 22 months | 21 months |
| 5-year survival | 19% | 20% | 21% | 15% | 22.5% | 22% |

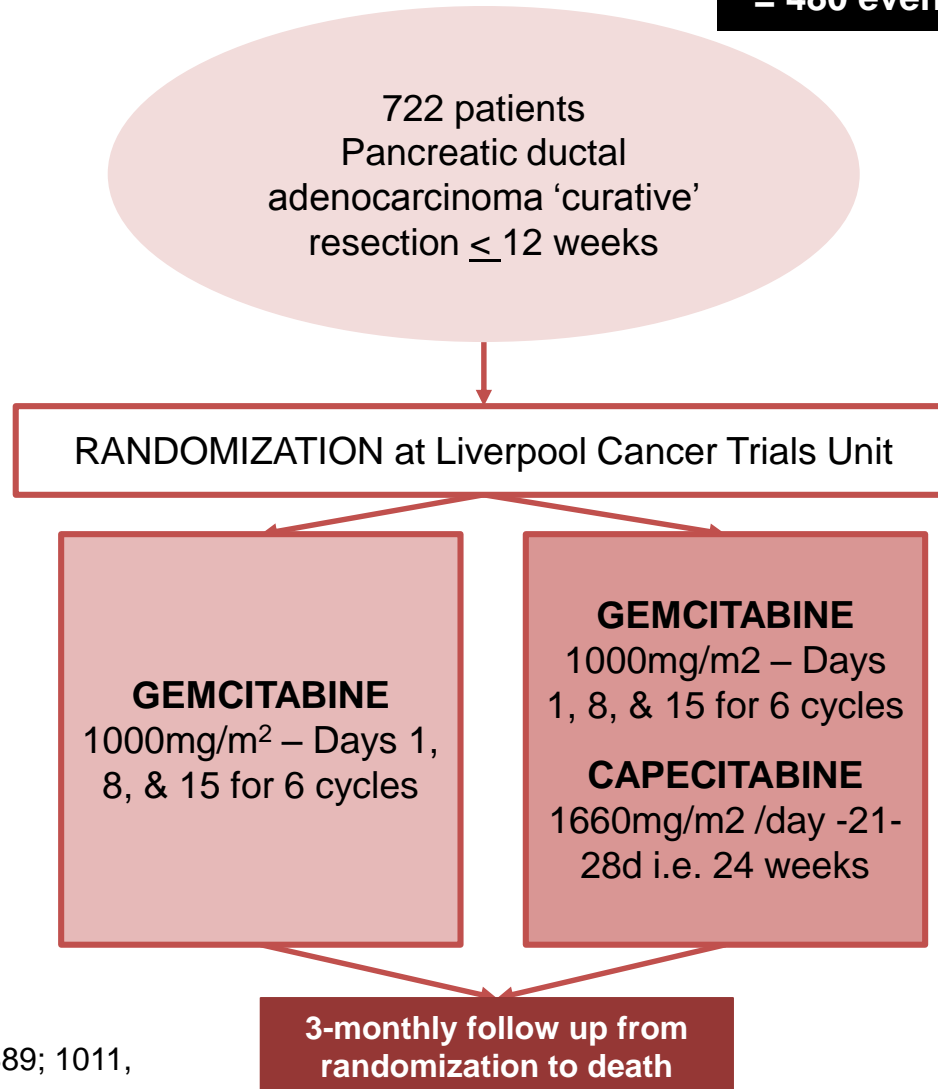
*Chemotherapy only group

[†]Includes patients with periampullary cancers

[‡]Among all patients

ESPAC-4 Trial

Stratified log-rank test with 5% 2-sided α ,
for a 10% difference in 2 year survival, 90%
power
= 480 events = 722 patients, 361 in @ arm

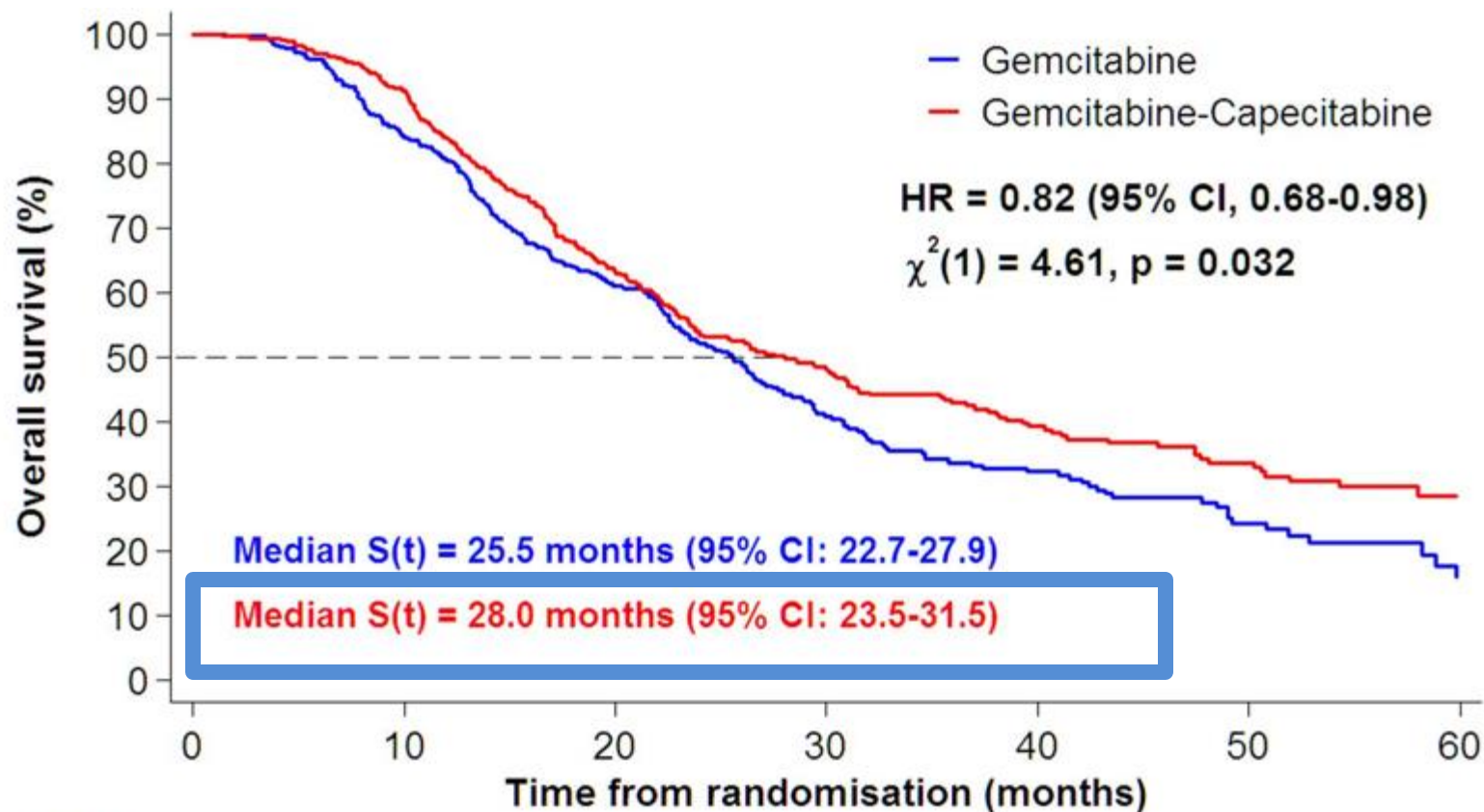


ESPAC-4: Patient Demographics

| | | GEM n=366 | GEMCAP n=364 | TOTAL n=730 |
|----------------------------------|---------|--------------|-----------------|----------------|
| *Age (years) | | 65 (37-80) | 65 (39-81) | 65(37-81) |
| Sex | Male | 212 (58%) | 202 (55%) | 414 (57%) |
| | Female | 154 (42%) | 162 (45%) | 316 (43%) |
| Baseline PS | 0 | 158 (43%) | 150 (41%) | 308 (42%) |
| | 1 | 199 (54%) | 202 (56%) | 401 (55%) |
| | 2 | 9 (3%) | 12 (3%) | 21 (3%) |
| Smoking | Never | 151 (41%) | 146 (40%) | 297 (41%) |
| | Past | 136 (37%) | 148 (41%) | 284 (39%) |
| | Present | 62 (17%) | 61 (17%) | 123 (17%) |
| | Unknown | 17 (5%) | 9 (2%) | 26 (3%) |
| *Surgery to Randomization (days) | | 65 (23-111) | 64 (21-111) | 64 (21-111) |

* Median (Range)

ESPAC-4: Overall Survival



No. at Risk

| | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|--------|-----|-----|-----|-----|----|----|----|
| Gem | 366 | 302 | 207 | 109 | 61 | 27 | 9 |
| GemCap | 364 | 328 | 219 | 139 | 83 | 50 | 19 |

ESPAC Trials: Summary of Results

| Trial | Treatment | Number of patients (N=2,092) | 5-Year OS (95% CI) | Stratified Log-Rank χ^2 | p-value |
|---------|-----------------------------|------------------------------|---------------------------|------------------------------|---------|
| ESPAC-1 | 5FU/FA | 149 | 21 (14.6–28.5) % | 7.03 | 0.030* |
| | No chemotherapy | 143 | 8.0 (3.8-14.1) % | | |
| | Chemoradiotherapy (5FU/Rad) | 145 | 10.8 (6.1-17.0) % | | |
| ESPAC-3 | GEM | 539 | 17.5 (14.0-21.2) % | 0.74 | 0.390* |
| ESPAC-4 | 5FU/FA | 551 | 15.9 (12.7-19.4) % | 4.61 | 0.032† |
| | GEM | 366 | 16.3 (10.2-23.7) % | | |
| | GEMCAP | 304 | 20.8 (22.9-33.2) % | | |

*Stratification factor: resection margin status; †stratification factors: resection margin status and country

ESPAC-4: Reported Toxicity

Number of patients in Safety Set with at least one NCI CTC v4 grade 3/4 event

| CTC 3/4 event | GEM | P-value* | GEMCAP |
|-----------------------------------|----------------------------------|----------|----------------------------------|
| | Number of patients (% of 366) | | Number of patients (% of 359) |
| Anaemia | 14 (4%) | 0.279 | 8 (2%) |
| Diarrhoea | 6 (2%) | 0.008 | 19 (5%) |
| Fatigue | 19 (5%) | 0.870 | 20 (6%) |
| Fever | 6 (2%) | 1.000 | 6 (2%) |
| Infection and infestations, Other | 24 (7%) | 0.012 | 9 (3%) |
| Lymphocytes | 11 (3%) | 0.821 | 9 (3%) |
| Neutrophils | 89 (24%) | <0.001 | 137 (38%) |
| Hand-Foot syndrome | 0 (0%) | <0.001 | 26 (7%) |
| Platelets | 7 (2%) | 0.800 | 8 (2%) |
| Thromboembolic event | 9 (2%) | 1.000 | 8 (2%) |
| WBC | 28 (8%) | 0.242 | 37 (10%) |

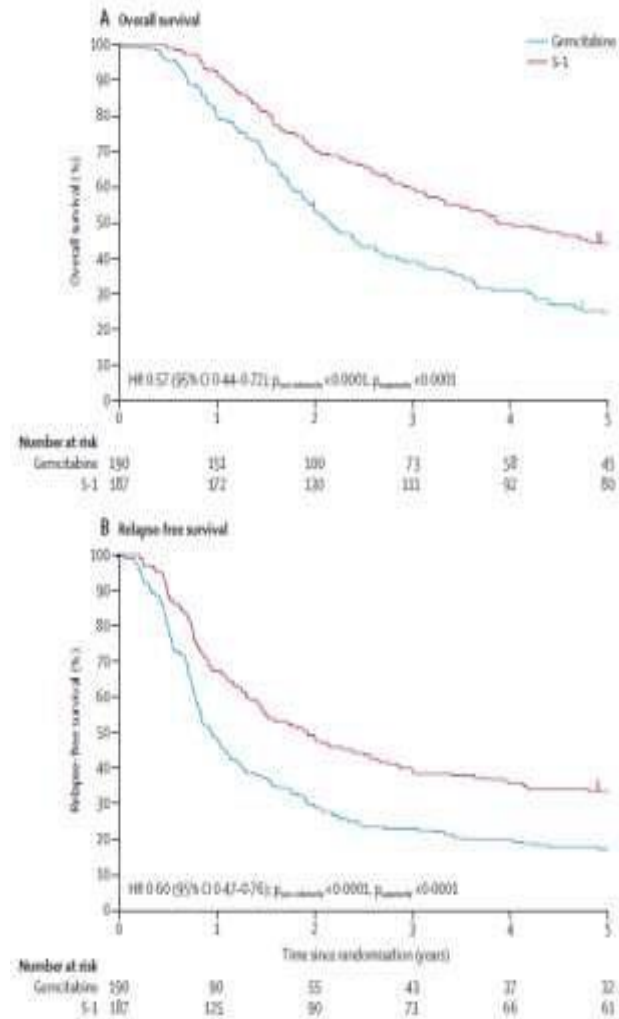
* Exploratory analysis: Fisher's exact test

Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01)



Katsuhiko Uesaka, Norikazu Boku, Akira Fukutomi, Yukiyo Okumura, Masaru Konishi, Apei Matsumoto, Yoji Kawase, Yoshihiro Shimizu, Shoji Nakazawa, Hirohiko Sakamoto, Soichiro Morinaga, Chayuu Kainuma, Koji Imai, Naohiro Sato, Shoichi Hishinuma, Heishi Ojima, Ryuzo Yamaguchi, Satoshi Hirano, Takeshi Sode, Yusuo Ohashi, for the JASPAC 01 Study Group

- N = 385
- S1 40-60 mg 2x/d for 4 / 6 weeks
- HR for S1: 0.57
- 5-y-OS rate:
 - S1: 43.6%
 - Gem: 24.2%
- G3/4 toxicity in favour of S1



Near Future in the Adjuvant Setting

- APACT: Gemcitabine plus nab-paclitaxel vs. gemcitabine alone
- NCT01526135/France: FOLFIRINOX vs. gemcitabine
- NCT02355119/Italy: FOLFOXIRI vs. gemcitabine

Conclusions

- Gemcitabine and capecitabine adjuvant therapy is a standard
- The role of adjuvant radiation therapy is controversial and ongoing adjuvant trials may help to clarify the uncertainty
- Neoadjuvant therapy is being tested as an alternative to upfront surgery.

Obrigado!!!!