# Current Management of Borderline Resectable & Locally Advanced Pancreatic Cancer

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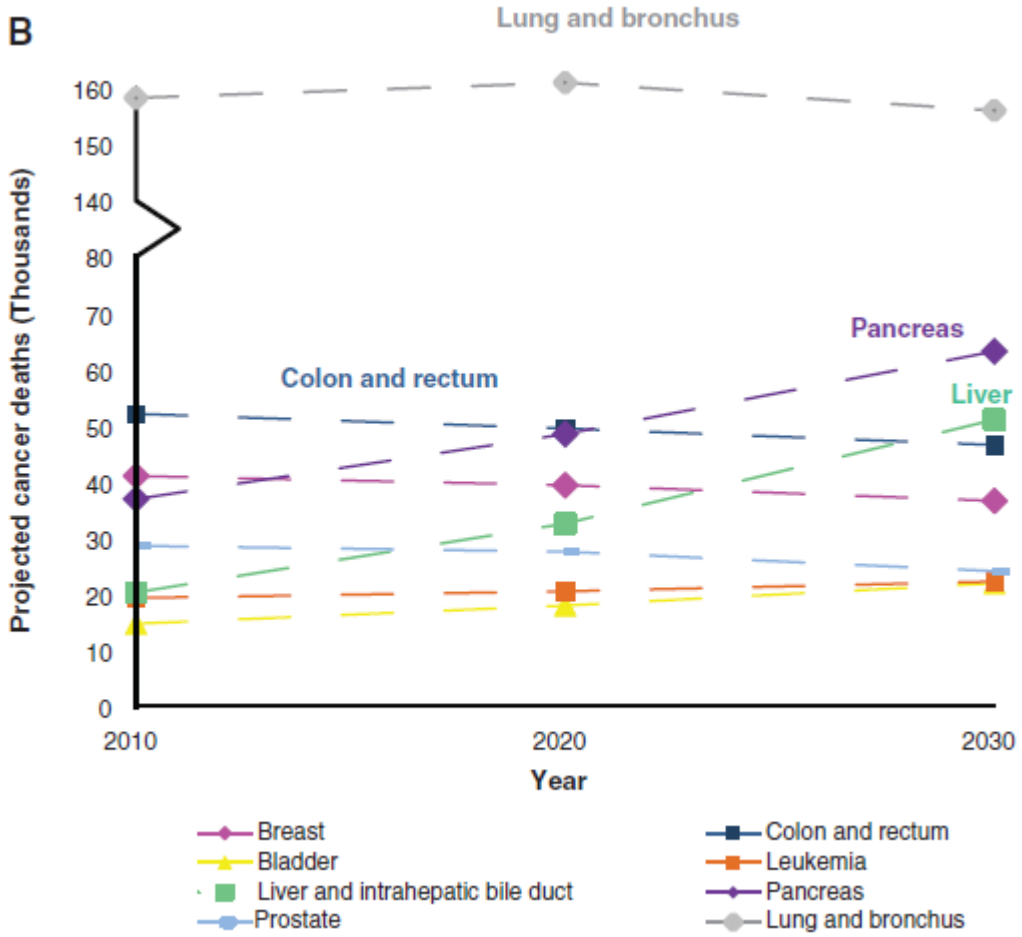
# DISCLOSURES

**Consultant:** Ipsen, Bristol Myers Squibb, Exelixis, Foundation Medicine, Terumo Interventional Systems, Taiho Oncology, Eisai, BTG (Boston Scientific), Roche/Genentech, France Foundation

**Research Support:** Roche/Genentech (Inst), Hoffman La-Roche (Inst), Taiho Oncology (Inst), Boehringer Ingelheim (Inst), Toray (Inst), NGM Biopharma (Inst) , Hutchison Medipharma (Inst), Mirati Therapeutics (Inst), CARsgen (Inst), Glyconex (Inst), Helix Biopharma (Inst), Pfizer (Inst), Transcenta (Inst), TVARDI(Inst)

# Pancreatic Cancer – Burden of Disease



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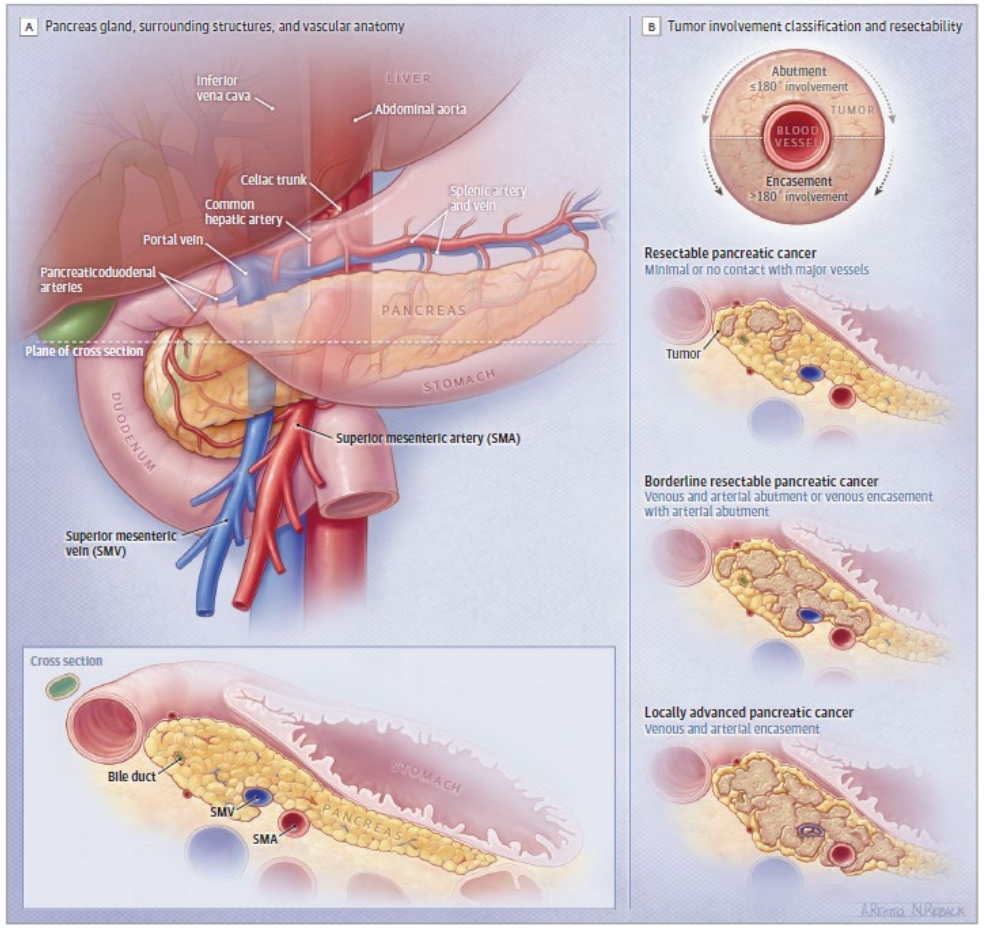
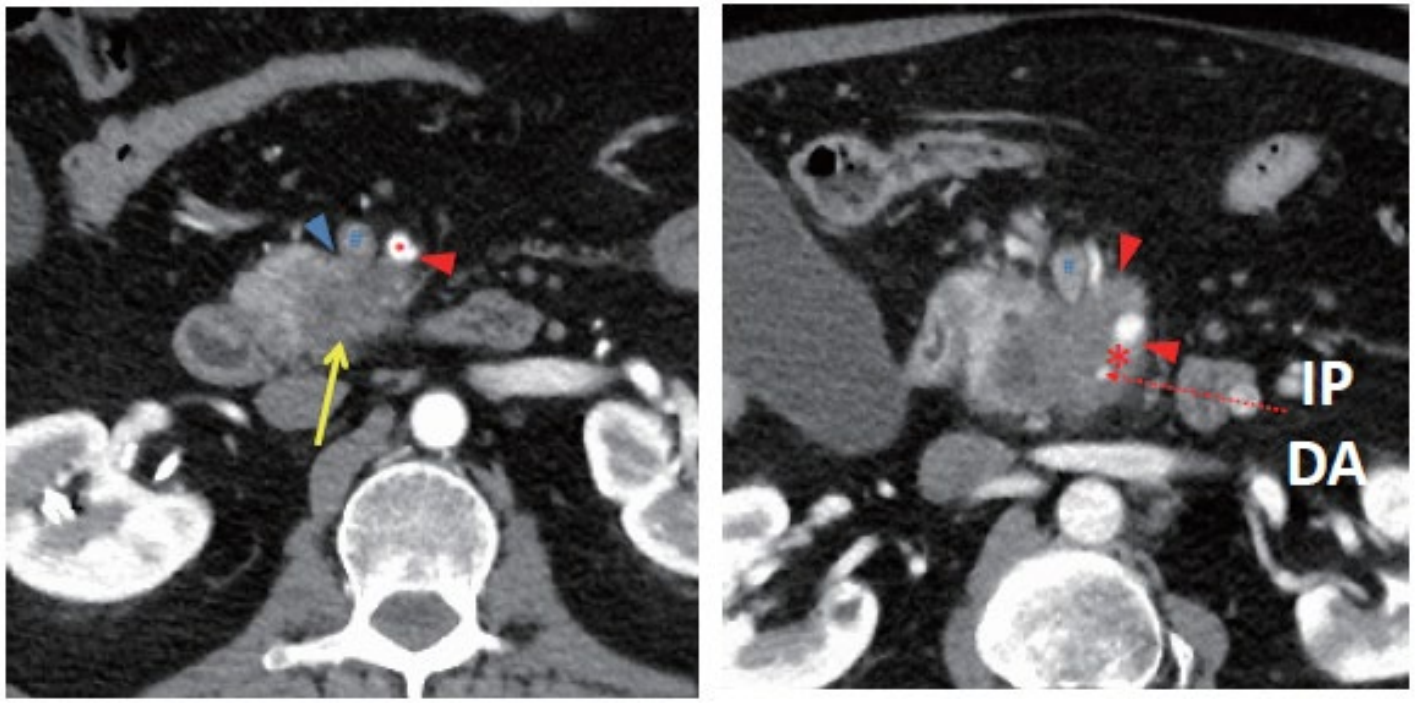
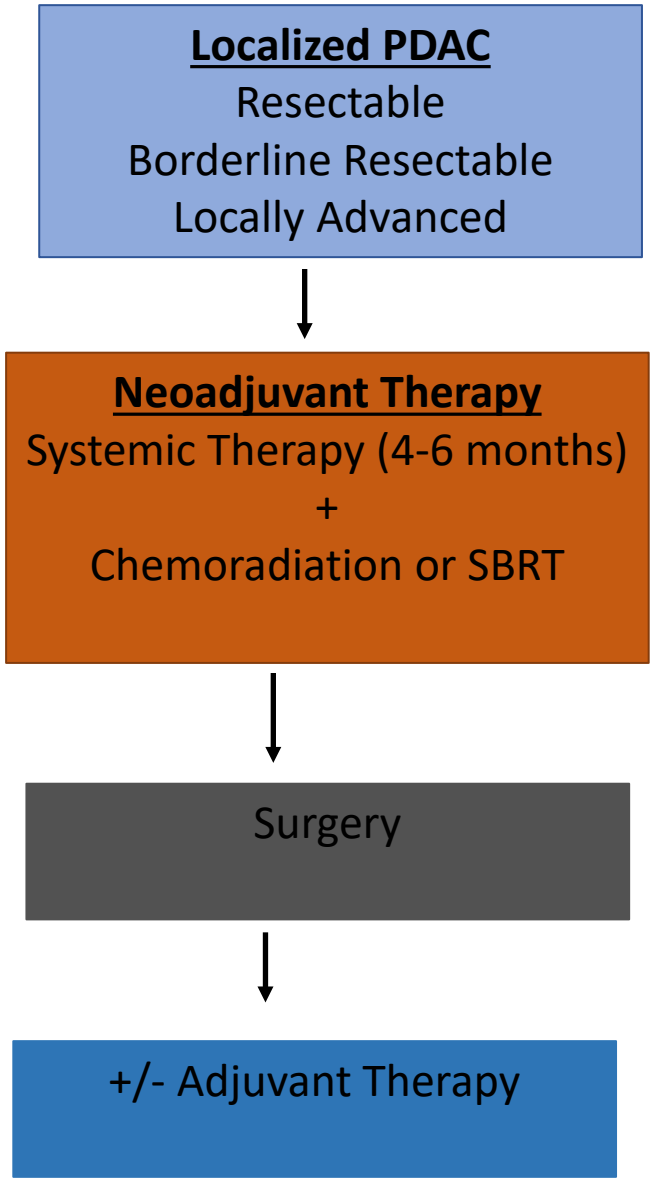
# Clinical Staging of Pancreatic cancer




Park, Chawla, and O'Reilly, JAMA 2021
Fathi, Christians, George, et. al, J. Gastrointest Oncol 2015

# Treatment Overview

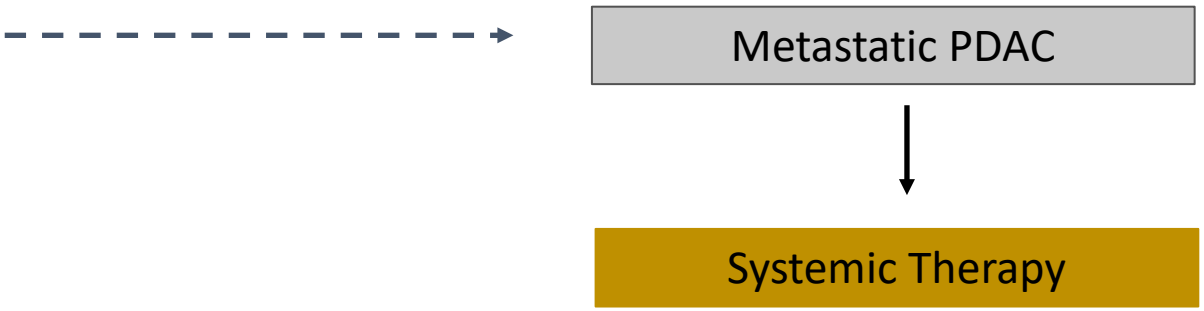



What is the Optimal Neoadjuvant Systemic Therapy?

Response Assessment to Neoadjuvant Therapy

Role of Radiation Therapy in the Treatment of BRPC and LAPC

Adjuvant Therapy after Neoadjuvant Therapy



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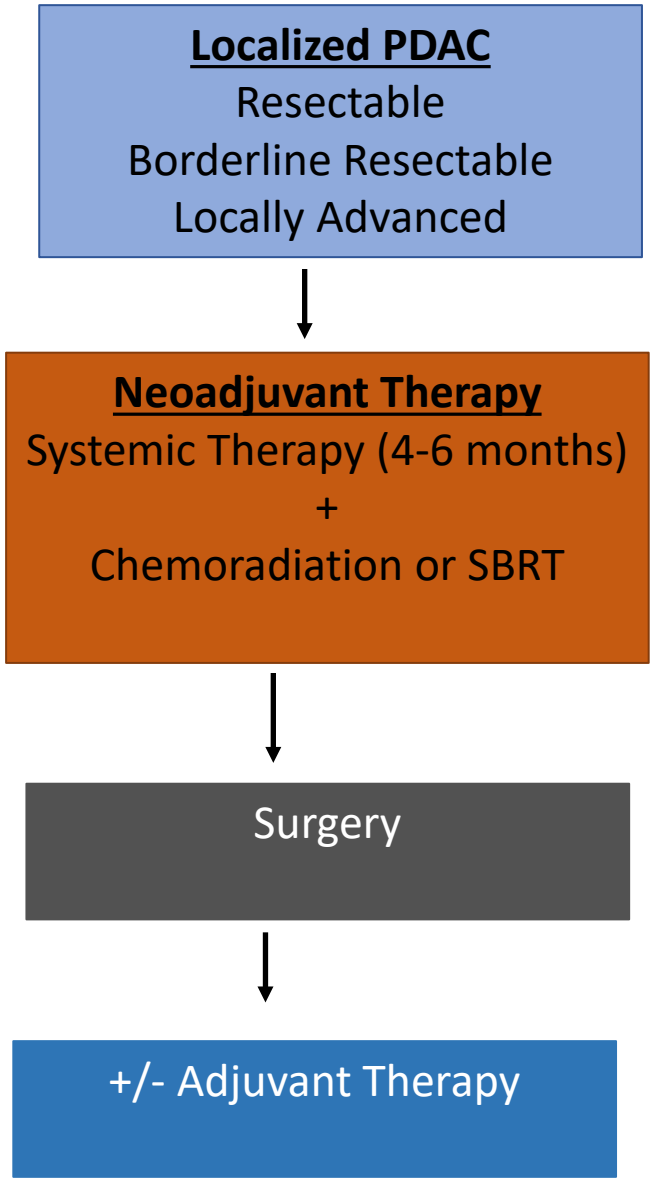


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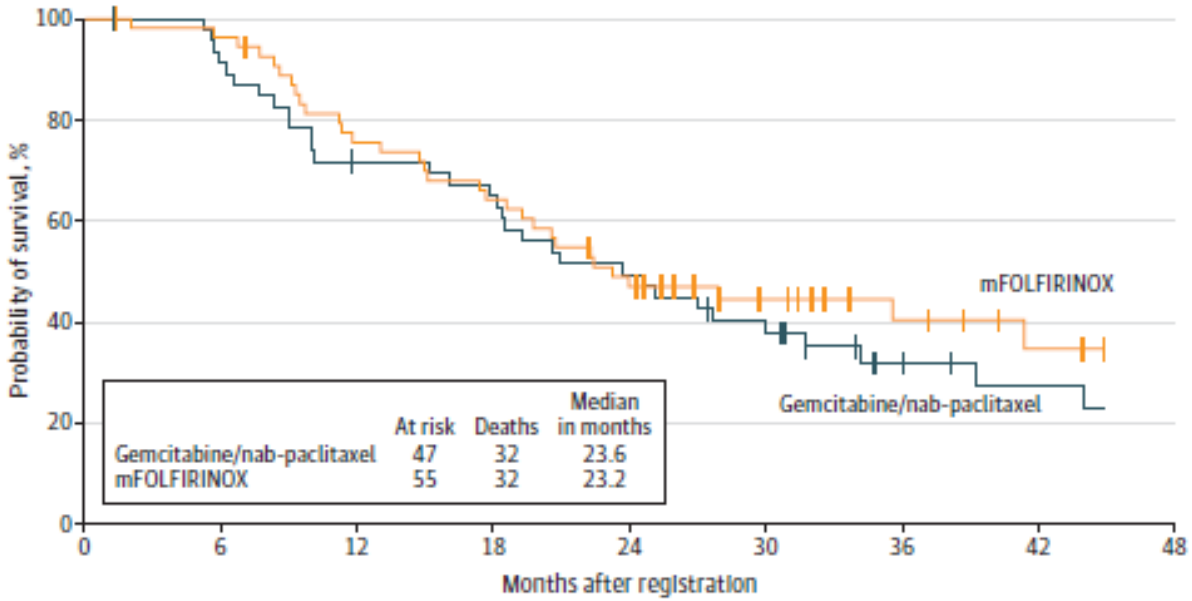
# FOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel Indirect Evidence – SWOG 1505




Sohal, Duong, Ahmad et. al, JAMA Oncology, 2021

# FOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel MDACC Experience

**Table 1. Clinical Profile of All 485 Included Patients**

| Characteristic | No. (%) of patients | | | P value |
|---|---|---|---|---|
| | | First-line chemotherapy regimen | | |
| | All (N = 485) | FOLFIRINOX (n = 285) | GA (n = 200) | |
| Sex | | | | |
| Female | 219 (45) | 125 (44) | 94 (47) | .50 |
| Male | 266 (55) | 160 (56) | 106 (53) | |
| Age at diagnosis | | | | |
| Median (range), y | 65 (30-89) | 61 (30-81) | 71 (36-89) | .001 |
| ≥75 y | | | | |
| Yes | 67 (14) | 11 (4) | 56 (28) | .001 |
| No | 418 (86) | 274 (96) | 144 (72) | |
| BMI, median (range) | 27 (16-56) | 27 (16-56) | 27 (18-50) | .20 |
| ECOG performance status | | | | |
| 2 | 439 (91) | 274 (96) | 165 (82) | .001 |
| ≥2 | 46 (9) | 11 (4) | 35 (18) | |
| Baseline CA 19-9 level, median (range), U/mL | 256 (1-39 800) | 256 (1-15 290) | 248 (1-39 800) | .90 |
| Tumor site | | | | |
| Head or neck | 367 (76) | 211 (74) | 156 (78) | .30 |
| Body or tail | 118 (24) | 74 (26) | 44 (22) | |
| Baseline radiographic stage | | | | |
| Resectable | 181 (37) | 91 (32) | 90 (45) | .01 |
| Borderline resectable | 133 (28) | 88 (31) | 45 (23) | |
| Locally advanced | 171 (35) | 106 (37) | 65 (32) | |
| No. of chemotherapy cycles | | | | |
| Mean | 6 | 5 | 6 | .01 |
| Median (range) | 5 (3-21) | 5 (3-13) | 5 (3-21) | |

Perri, Prakash, Qiao et. al, JAMA Surgery, 2020

# FOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel
# MDACC Experience

**Table 2. Metrics of Response to Chemotherapy Among All 485 Included Patients**

| Characteristic | No. (%) of patients | | | *P* value |
|---|---|---|---|---|
| | All (N = 485) | First-line chemotherapy regimen | | |
| | | FOLFIRINOX (n = 285) | GA (n = 200) | |
| Radiographic measures after treatment | | | | |
| Reduction in primary tumor volume | | | | |
| Yes | 324 (67) | 189 (66) | 135 (67) | .80 |
| No | 161 (33) | 96 (34) | 65 (33) | |
| %Δvol, Median (range) | 20 (−297 to 92) | 21 (−297 to 90) | 15 (−227 to 92) | .50 |
| RECIST 1.1 | | | | |
| CR | 0 | 0 | 0 | .40 |
| PR | 55 (11) | 37 (13) | 18 (9) | |
| SD | 382 (79) | 219 (77) | 163 (82) | |
| PD[a] | 48 (10) | 29 (10) | 19 (9) | |
| Local tumor downstaging[b] | | | | |
| Yes[c] | 17 (6) | 10 (5) | 7 (6) | .60 |
| No[c] | 287 (94) | 181 (95) | 103 (94) | |

**Table 3. Metrics of Response to Chemotherapy Among 280 Matched Patients**

| Characteristic | No. (%) of patients | | | *P* value |
|---|---|---|---|---|
| | All (n = 280) | First-line chemotherapy regimen | | |
| | | FOLFIRINOX (n = 140) | GA (n = 140) | |
| Radiographic measures after treatment | | | | |
| Reduction in primary tumor volume | | | | |
| Yes | 197 (70) | 100 (71) | 97 (69) | .70 |
| No | 83 (30) | 40 (29) | 43 (31) | |
| %Δvol, Median (range) | 20 (−240 to 90) | 30 (−240 to 90) | 10 (−150 to 90) | .10 |
| RECIST 1.1 | | | | |
| CR | 0 | 0 | 0 | .001 |
| PR | 35 (13) | 27 (19) | 8 (6) | |
| SD | 219 (78) | 102 (73) | 117 (83) | |
| PD | 26 (9) | 11 (8) | 15 (11) | |
| Local tumor downstaging[a] | | | | |
| Yes[b] | 13 (8) | 7 (8) | 6 (7) | .70 |
| No[b] | 154 (92) | 79 (92) | 75 (93) | |

Perri, Prakash, Qiao et. al, JAMA Surgery, 2020

# FOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel MDACC Experience

**Table 4. Univariate and Multivariate Cox Proportional Hazards Regression Analysis of Overall Survival for All 485 Patients**

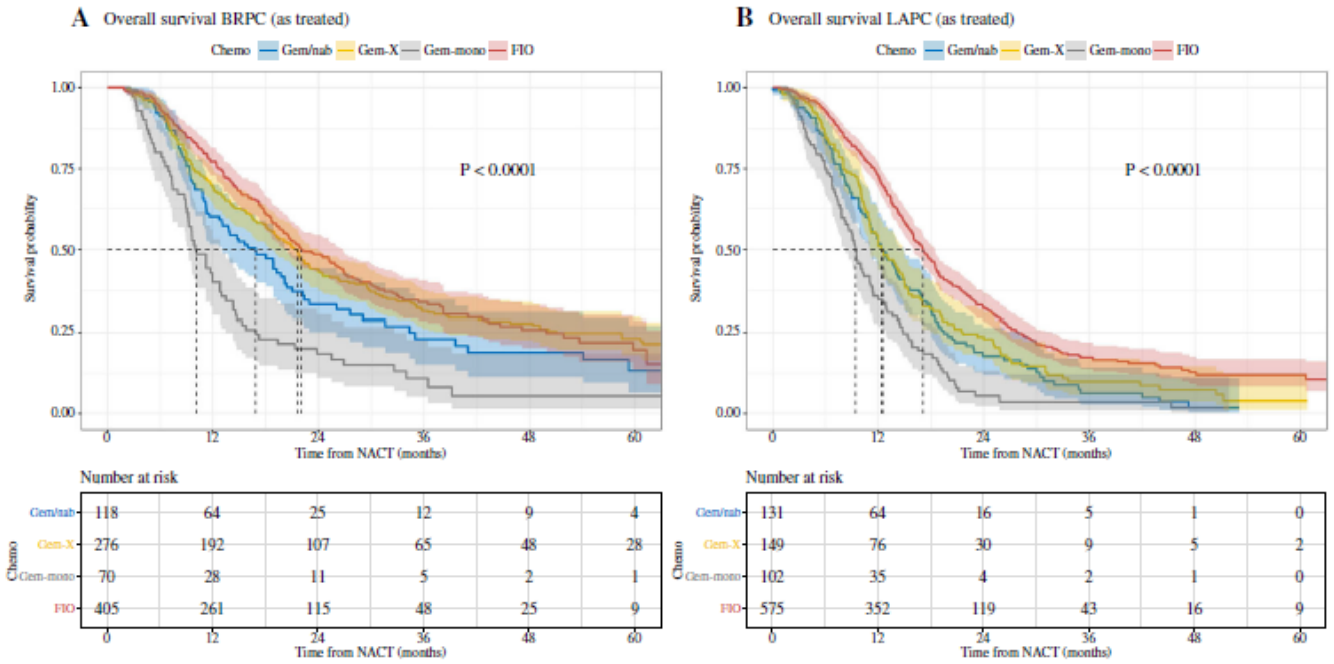
| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Characteristic | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Female sex | 1.08 (0.86-1.35) | .50 | NA | NA |
| BMI | 1.01 (0.98-1.02) | .60 | NA | NA |
| Age ≥75 y | 0.98 (0.69-1.37) | .90 | NA | NA |
| ECOG PS ≥2 | 1.37 (0.95-1.97) | .09 | 1.47 (1.01-2.13) | .04 |
| First-line chemotherapy regimen | | | | |
| FOLFIRINOX | 1 [Reference] | NA | NA | NA |
| GA | 0.91 (0.72-1.15) | .50 | 1.14 (0.89-1.44) | .30 |
| Baseline CA 19-9 level | 1.01 (1.00-1.01) | .001 | 1.01 (1.00-1.01) | .001 |
| Tumor site | | NA | NA | |
| Body or tail | 1 [Reference] | NA | NA | |
| Head or neck | 0.96 (0.74-1.25) | .50 | NA | |
| Baseline radiographic stage | | NA | NA | |
| Resectable | 0.70 (0.54-0.91) | .001 | 0.60 (0.45-0.80) | .001 |
| Borderline resectable | 0.86 (0.65-1.15) | .30 | 0.79 (0.59-1.06) | .10 |
| Locally advanced | 1 [Reference] | NA | NA | NA |
| No. of chemotherapy cycles | 0.95 (0.91-0.99) | .03 | 0.92 (0.88-0.96) | .001 |

**Table 5. Univariate and Multivariate Cox Proportional Hazards Regression Analysis of Overall Survival for 280 Matched Patients**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Characteristic | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Female sex | 1.19 (0.67-2.13) | .50 | NA | NA |
| BMI | 1.01 (0.96-1.07) | .70 | NA | NA |
| First-line chemotherapy regimen | | | | |
| FOLFIRINOX | 1 [Reference] | | | |
| GA | 1.50 (1.00-2.26) | .05 | 1.48 (0.97-2.26) | .07 |
| Baseline CA 19-9 level, U/mL | 1.01 (0.99-1.03) | .30 | NA | NA |
| Tumor site | | | | |
| Head or neck | 1 [Reference] | | | |
| Body or tail | 0.78 (0.39-1.56) | .50 | NA | NA |
| No. of chemotherapy cycles | 0.72 (0.52-1.01) | .06 | 0.73 (0.52-1.02) | .06 |

Perri, Prakash, Qiao et. al, JAMA Surgery, 2020

# FOLFIRINOX vs. Gemcitabine/Nab-Paclitaxel Patient Level Meta-analysis




Eshmuminov, Aminjonov, Palm et. al, Annals of Surgical Oncology, 2023

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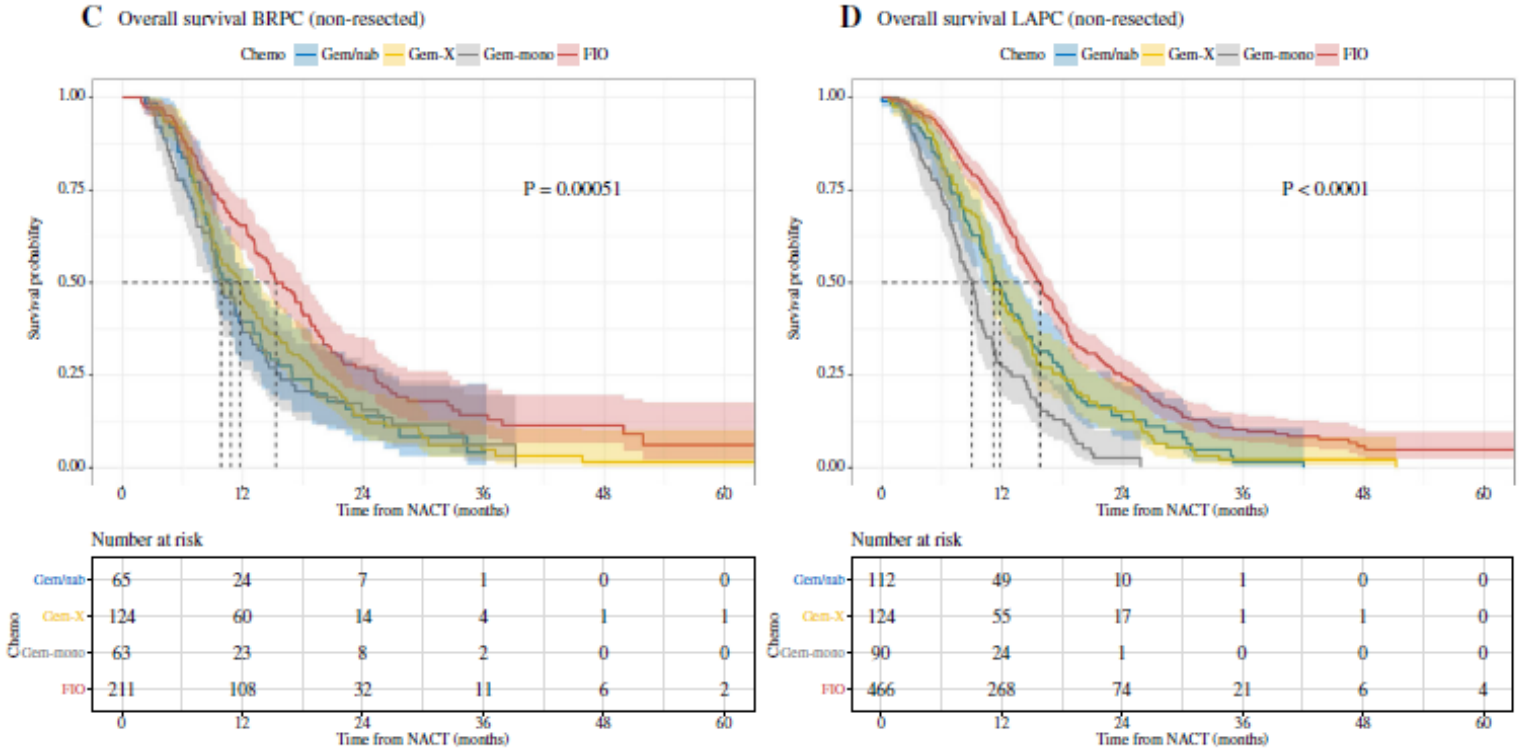


Eshmuminov, Aminjonov, Palm et. al, Annals of Surgical Oncology, 2023

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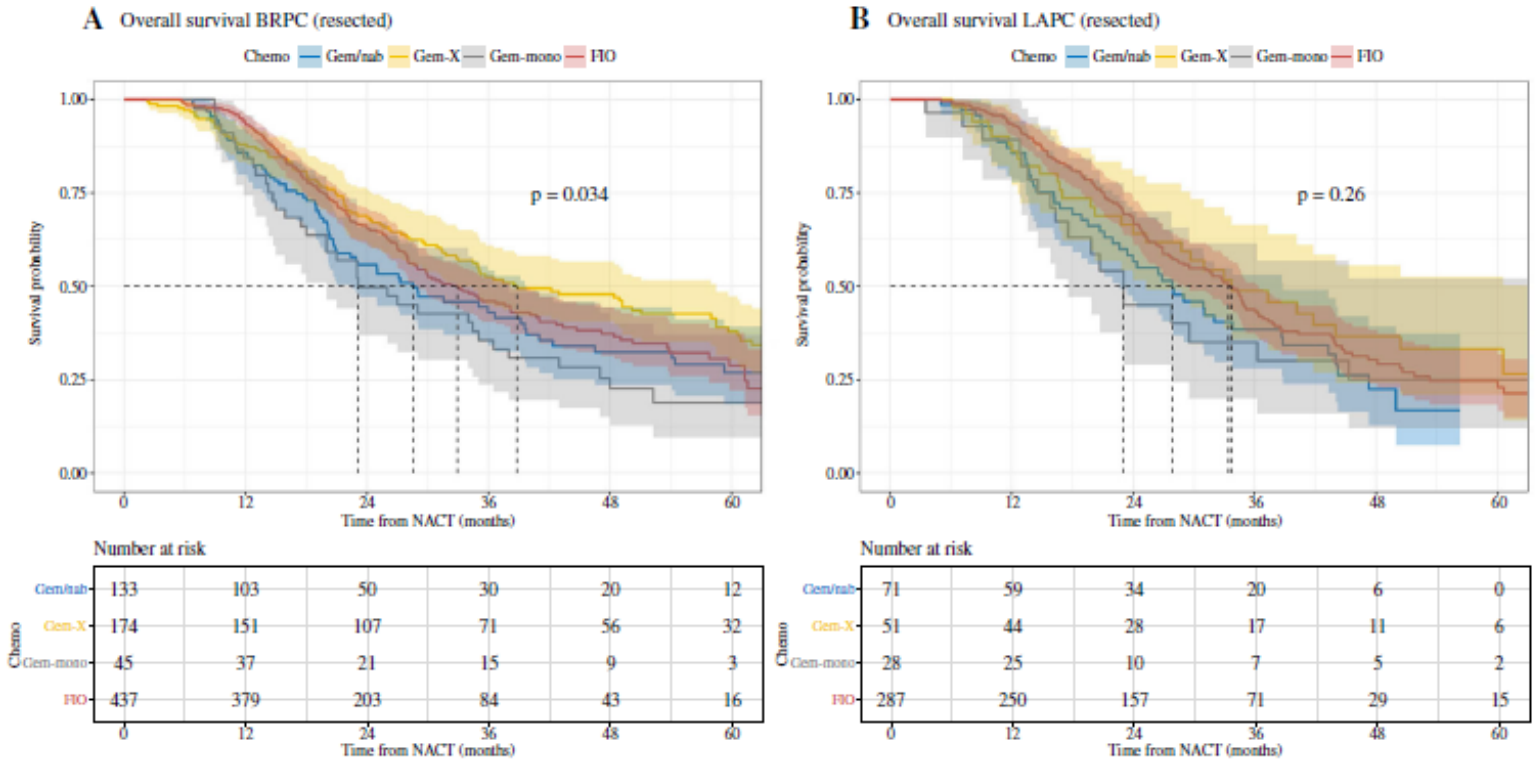


Eshmuminov, Aminjonov, Palm et. al, Annals of Surgical Oncology, 2023

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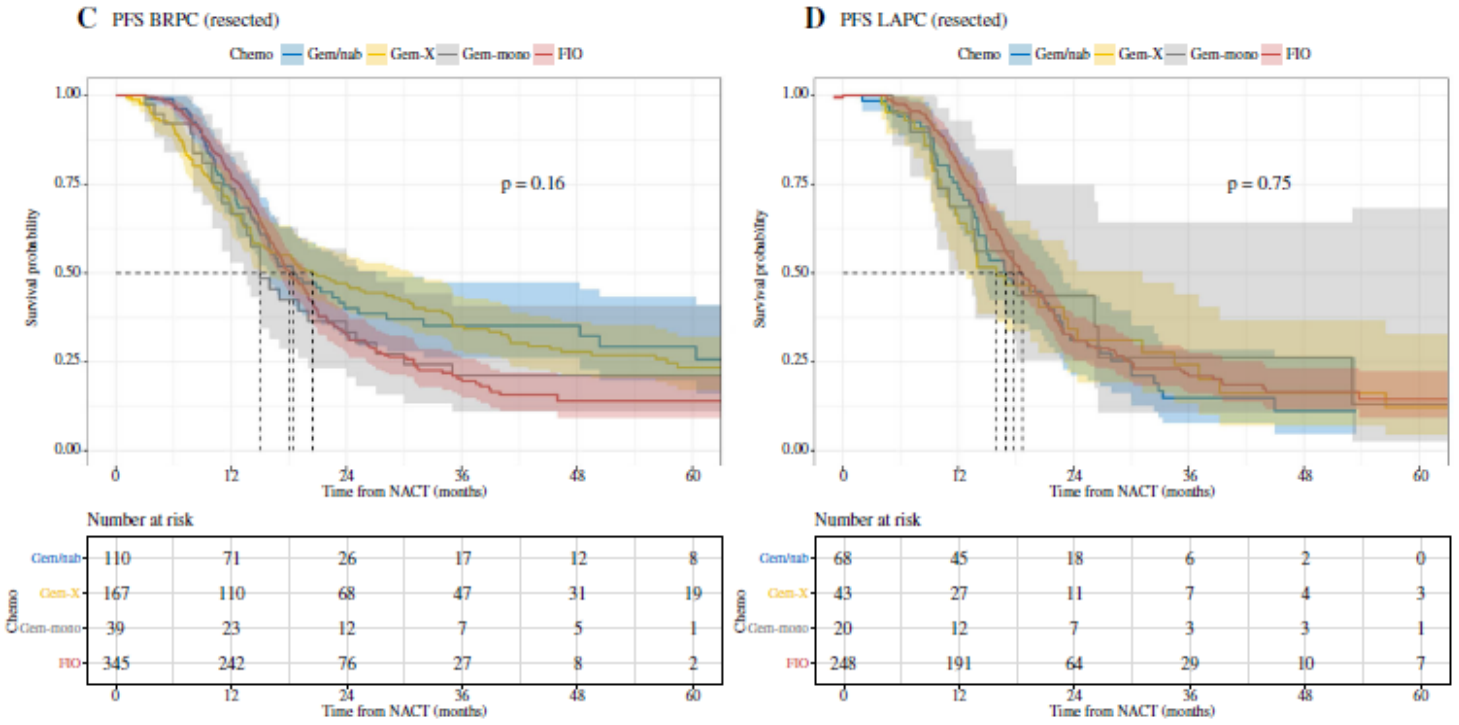




Eshmuminov, Aminjonov, Palm et. al, Annals of Surgical Oncology, 2023

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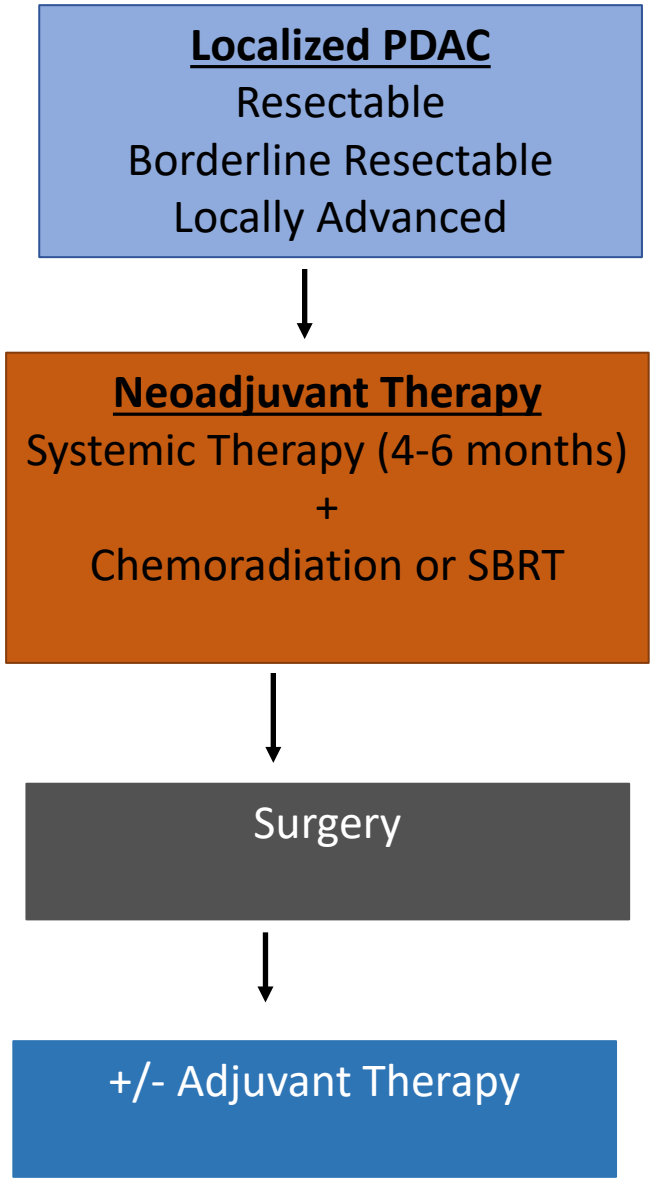
# Treatment Overview

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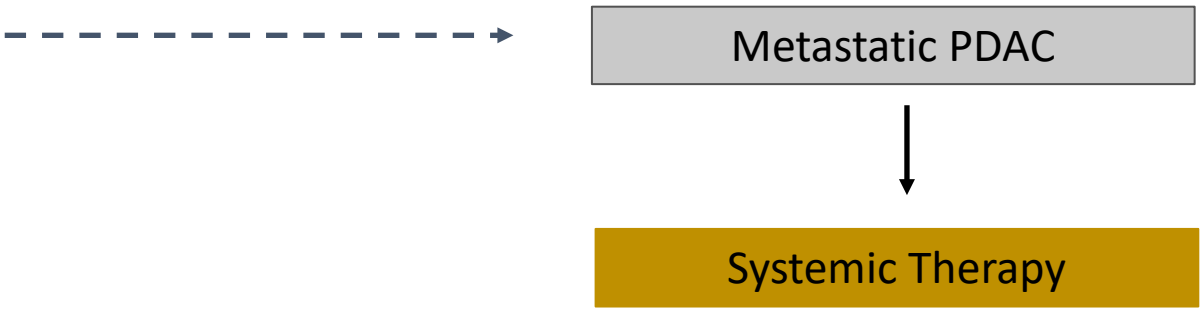




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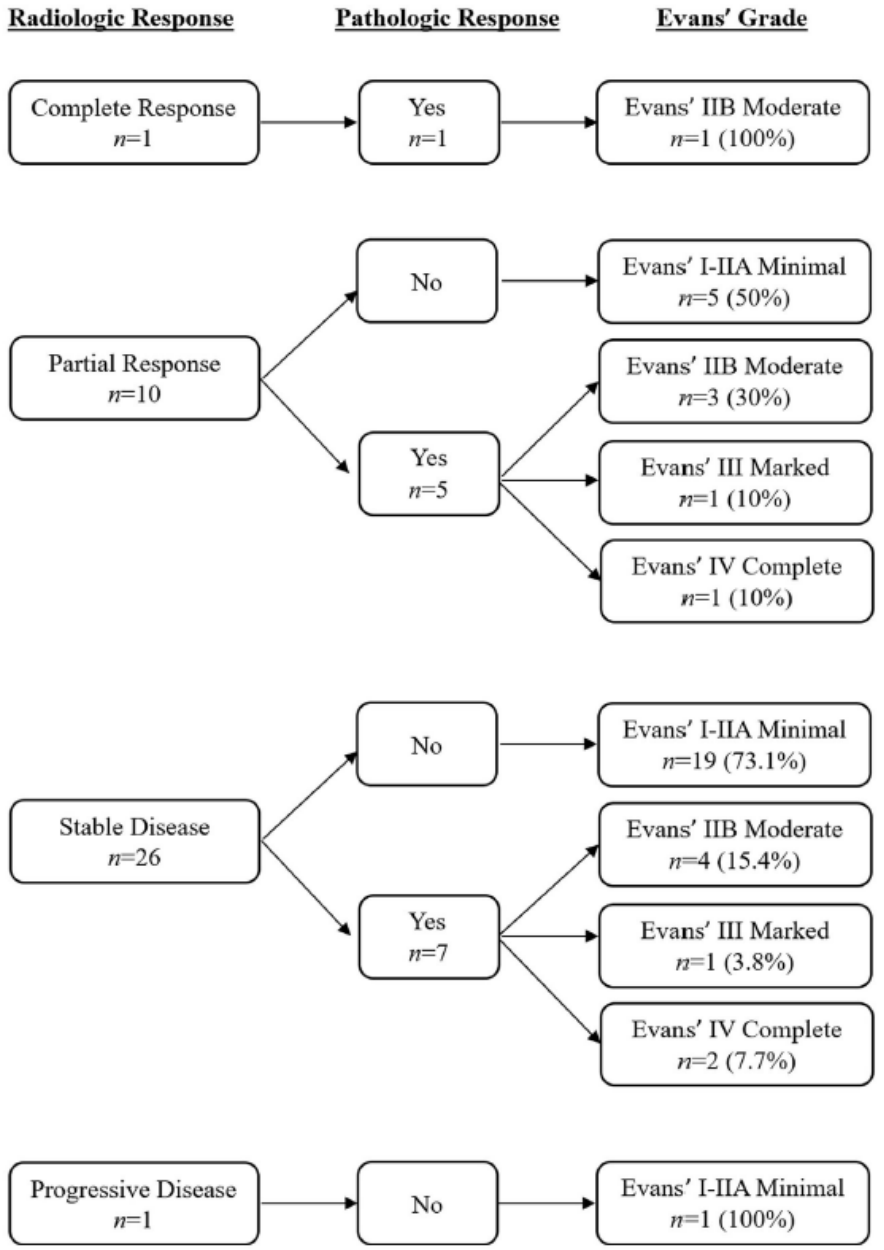
# Radiologic Response vs. Pathologic Response




Xia, Fu, Wang et. al, Journal of Surgical Oncology, 2021

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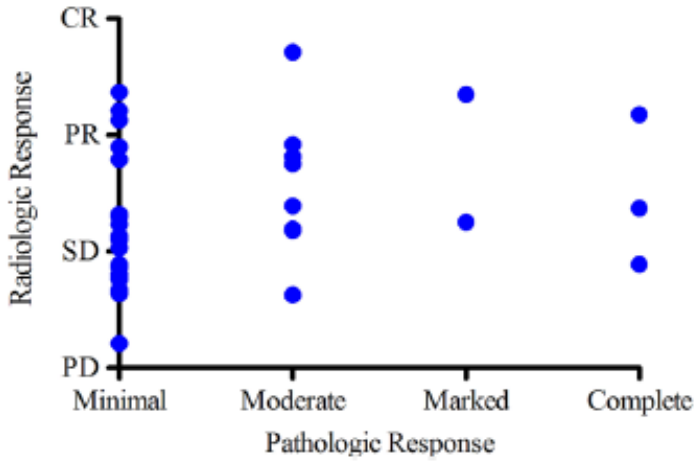
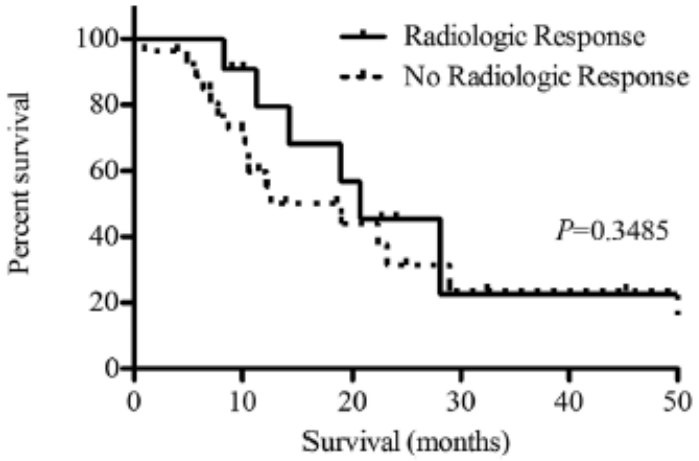
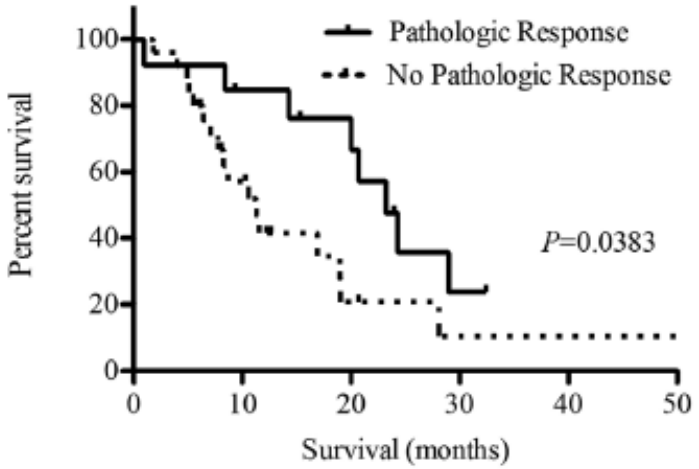
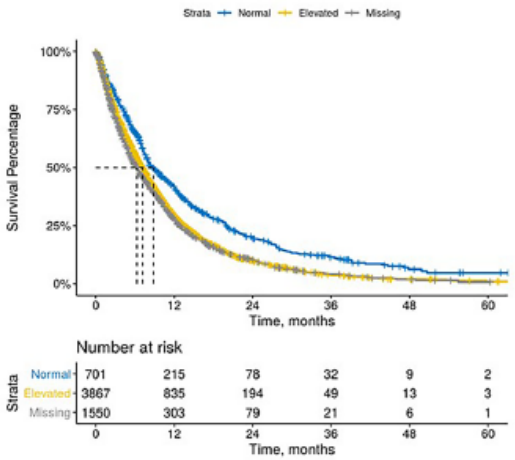



Xia, Fu, Wang et. al, Journal of Surgical Oncology, 2021

# CA 19-9 –Metastatic Disease



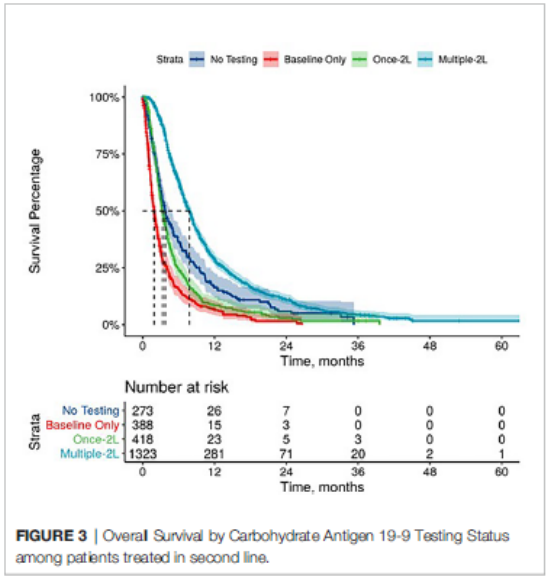




**FIGURE 3** | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in second line.

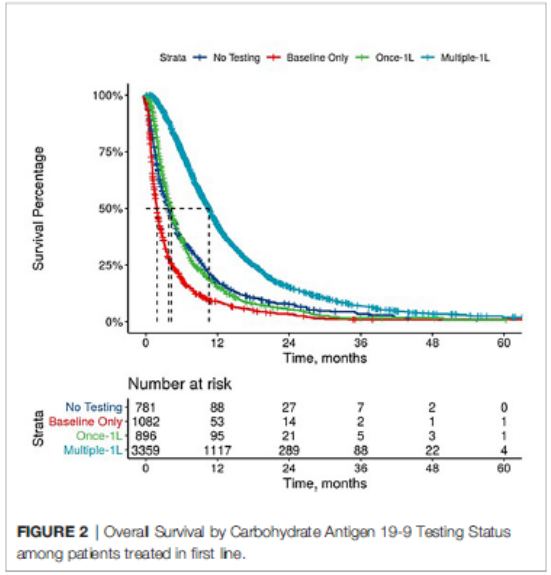



**FIGURE 2** | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in first line.

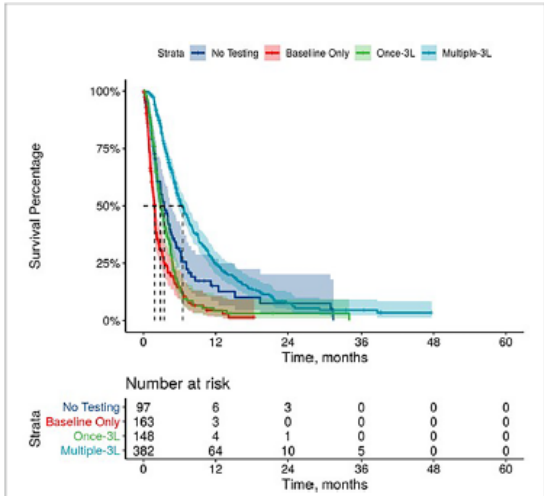



**FIGURE 4** | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in third line.

George, Kent, Surinach et. al, Frontiers in Oncology, 2021



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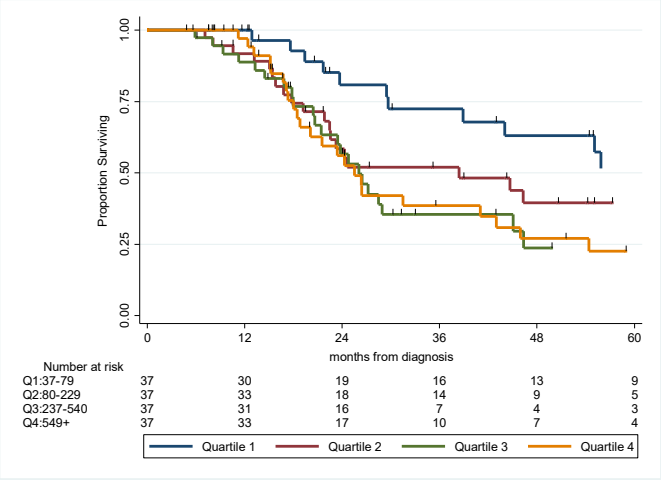
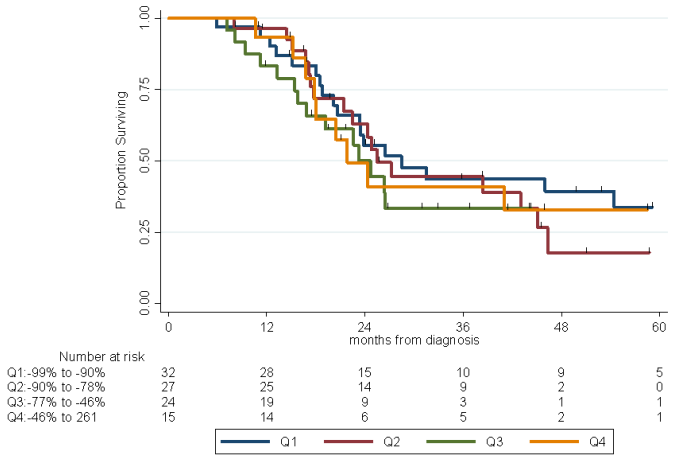
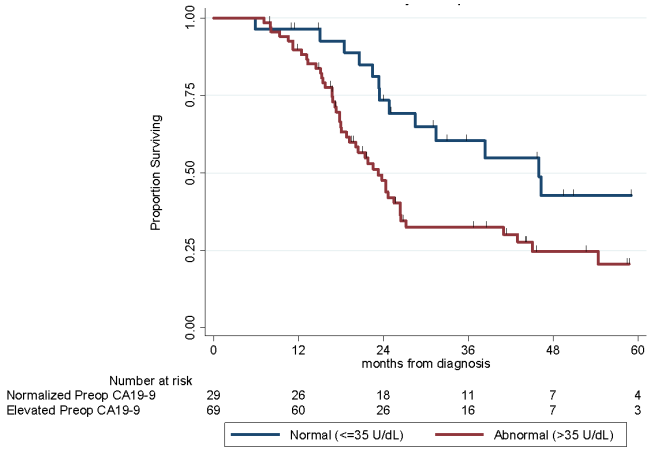
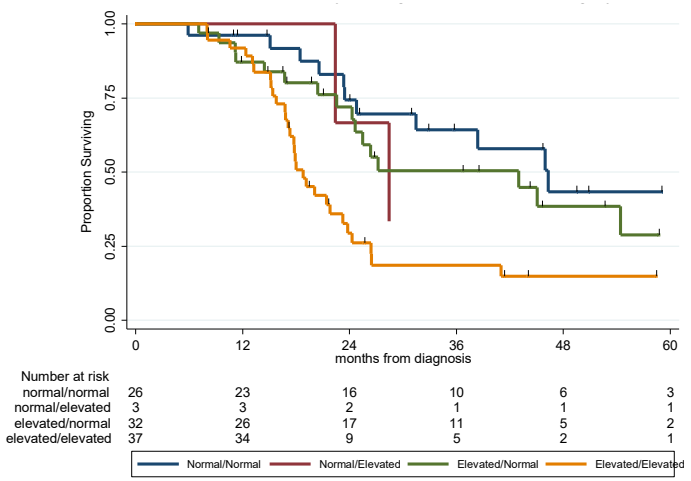
# CA 19-9 – Localized disease




Tsai, George, Wittman et. al, Annals of Surgery, 2018



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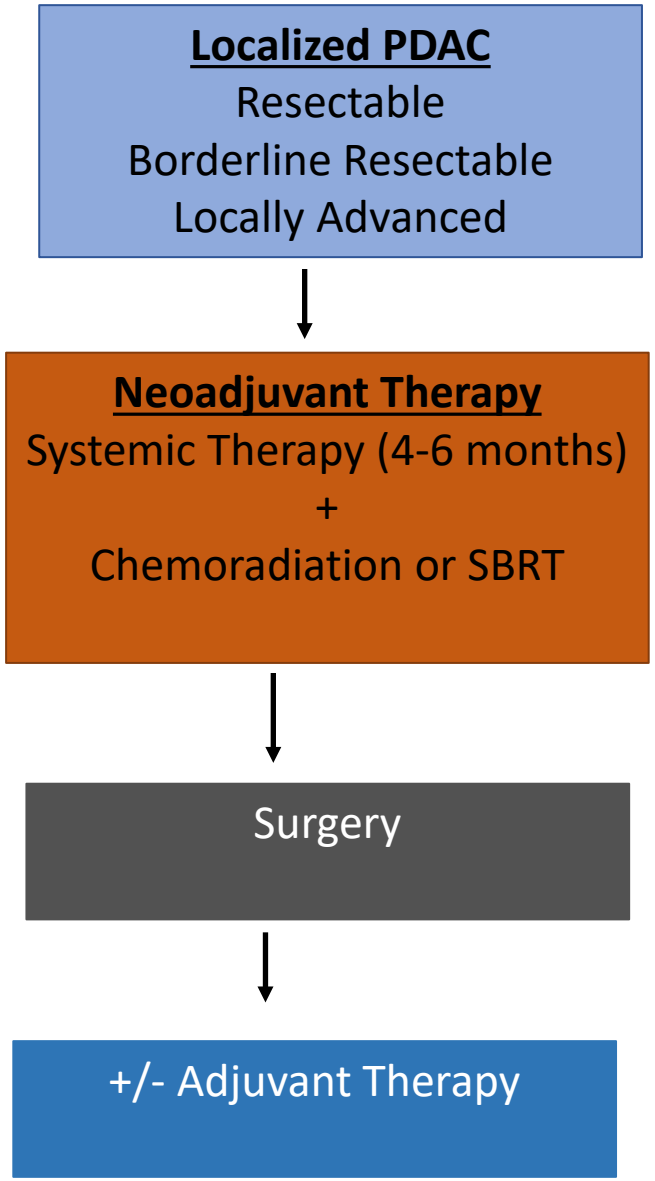
# Summary

- The goal of neoadjuvant systemic therapy is elimination of micro-metastatic disease more than local tumor regression
- FOLFIRINOX is the preferred neoadjuvant systemic chemotherapy program
  - patients with HRD (or high likelihood of HRD and excellent PS)
- Gemcitabine/Nab-paclitaxel is a very reasonable neoadjuvant systemic chemotherapy program
- Early and frequent response assessment is key
- Plasticity of the tumor micro-environment may dictate switching systemic therapy programs in the peri-operative setting
- Clinical trials aimed at optimizing systemic therapies in the peri-operative setting is crucial
  - Less clonally evolved tumors and increased likelihood of cure

# Treatment Overview

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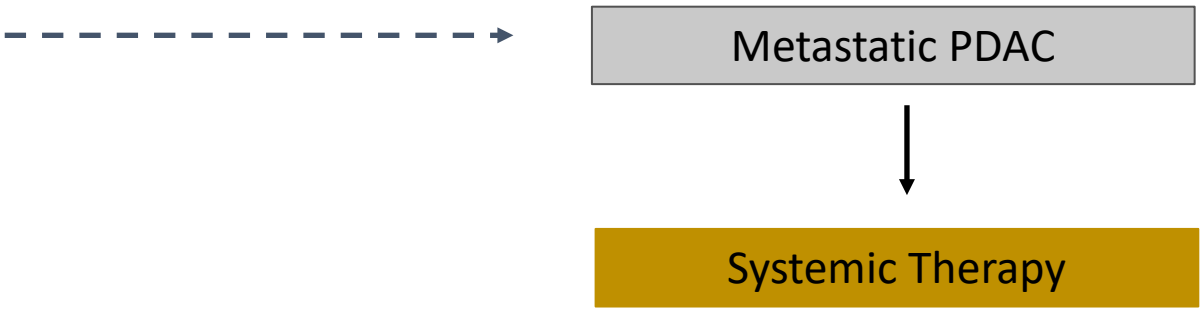




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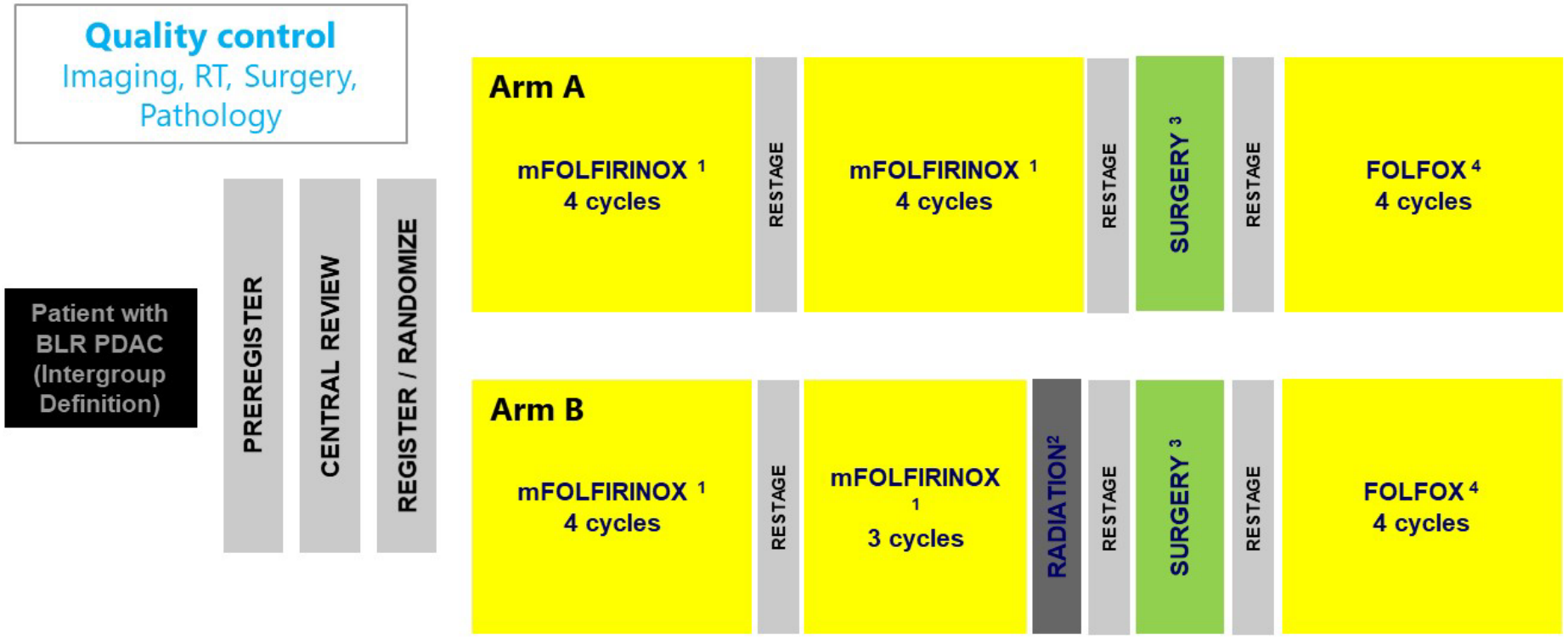
# Alliance A021501




[1] Oxaliplatin 85 mg/m$^2$, irinotecan 180 mg/m$^2$, leucovorin 400 mg/m$^2$ and infusional 5-fluorouracil 2400 mg/m$^2$ over 46 h
[2] Stereotactic Body RT, 33-40 Gy in 5 fx or hypofractionated image guided RT, 25 Gy in 5 fx
[3] Segmental pancreatectomy with regional lymphadenectomy +/- vascular resection
[4] Oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$ and infusional 5-fluorouracil 2400 mg/m$^2$ over 46 h

Katz, Shi, Myers et. al, JAMA Oncology, 2022
Figure adaptation from Hong TS, ASCO presentation

# Alliance A021501

**Baseline clinicodemographic profile of all treated patients**

| Characteristic | Arm A mFOLFIRINOX (n = 65) | Arm B mFOLFIRINOX → RT (n = 55) |
|---|---|---|
| Age, yr, median (range) | 62 (37 – 83) | 64 (40 – 80) |
| Female gender, n (%) | 32 (49) | 28 (51) |
| White race, n (%) | 54 (83) | 50 (91) |
| ECOG 0, n (%) | 33 (51) | 32 (58) |
| CA 19-9, U/ml, median (range) | 167 (1 – 13,220) | 260 (0 – 14,010) |

Katz, Shi, Myers et. al, JAMA Oncology, 2022
Figure adaptation from Hong TS, ASCO presentation

# Alliance A021501

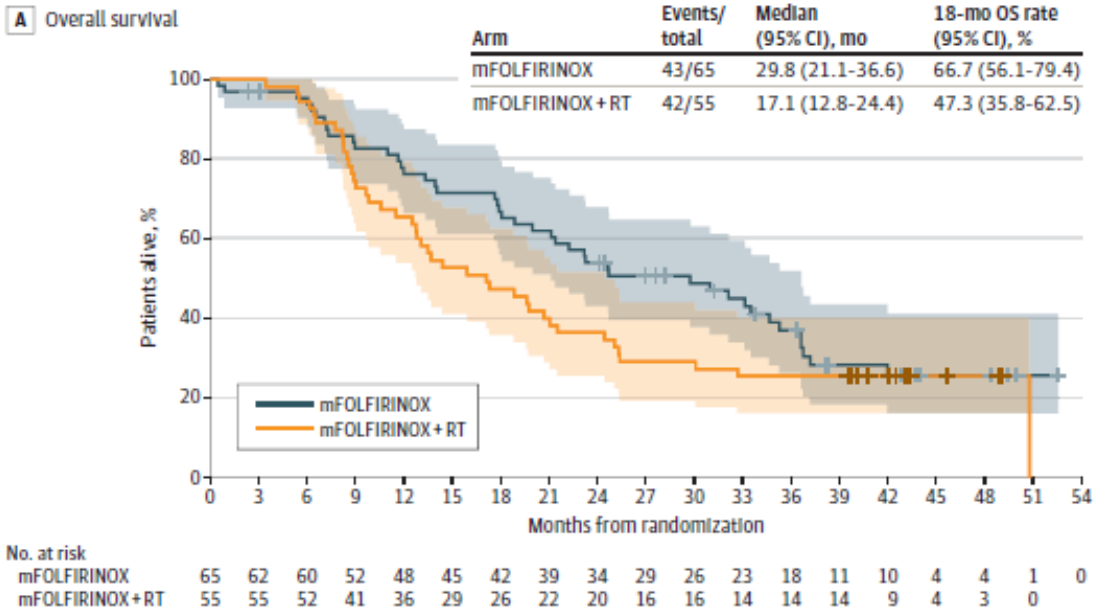
**Surgery and pathology outcomes**

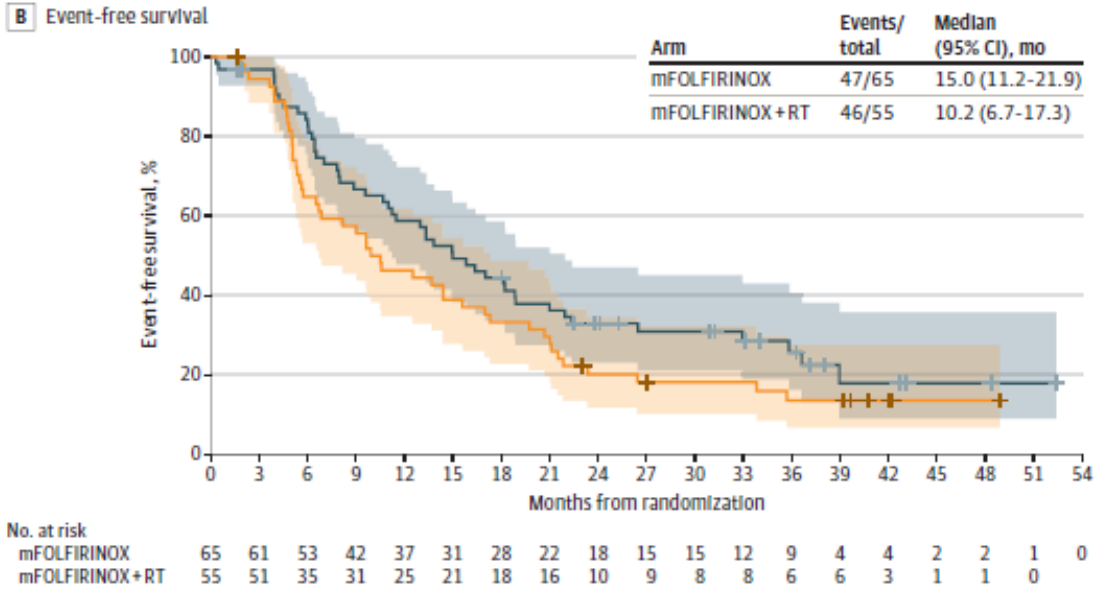
| Characteristic, n (%) | Arm A mFOLFIRINOX (n = 32) | Arm B mFOLFIRINOX → RT (n = 19) |
|---|---|---|
| Pancreatoduodenectomy | 30 (94) | 18 (95) |
| SMV/PV resection | 12 (38) | 6 (32) |
| Hepatic artery resection | 1 (3) | 2 (11) |
| R0, n (%) | 28 (88) | 14 (74) |
| N0, n (%) | 15 (47) | 9 (47) |
| pCR | 0 | 2 (11) * |

* < 5% viable cancer cells: Arm A 4 (13%); Arm B 5 (26%)

Katz, Shi, Myers et. al, JAMA Oncology, 2022
Figure adaptation from Hong TS, ASCO presentation

# Alliance A021501




Katz, Shi, Myers et. al, JAMA Oncology, 2022
Figure adaptation from Hong TS, ASCO presentation



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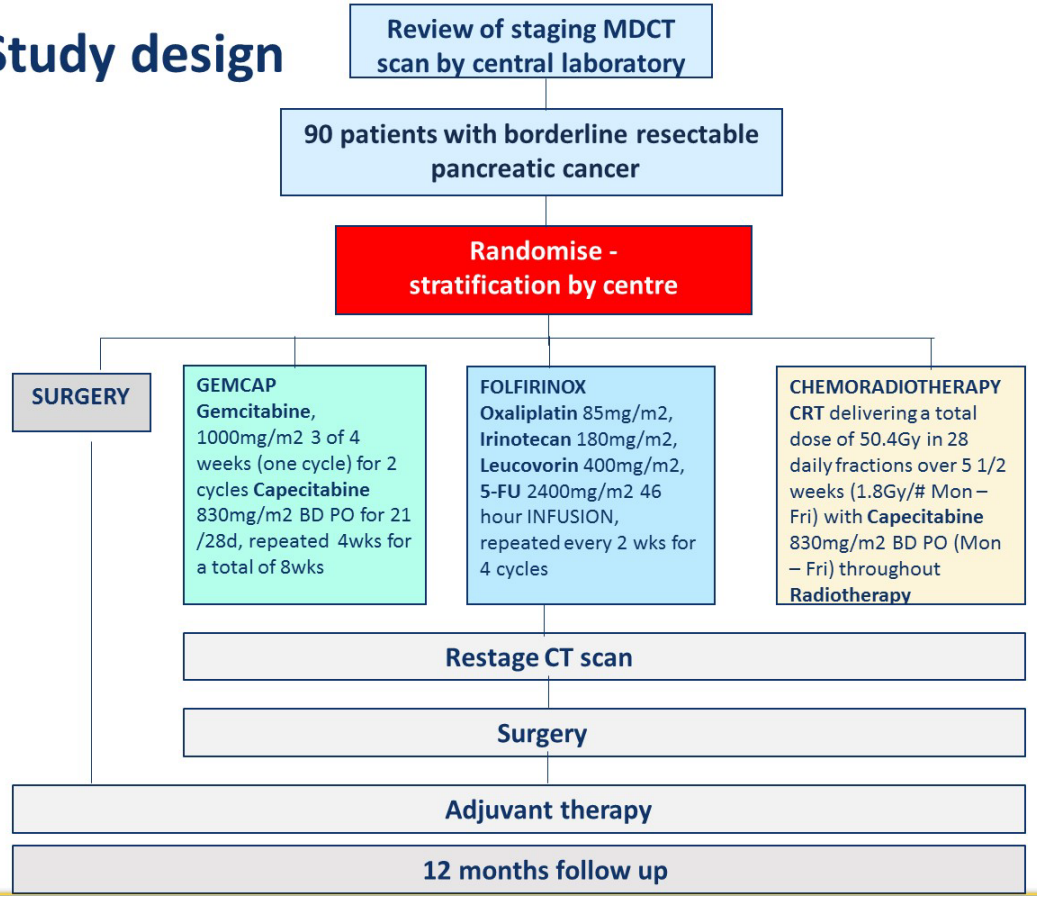
# ESPAC-5F: Four arm, prospective, multicentre, international randomised phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer.

## Study design




**Primary**
1. Recruitment rate
2. Resection rate (R1 + R0)

**Secondary**
1. R0 resection margin rate
2. Toxicity
3. Overall survival
4. Post operative complication rate
5. Post operative mortality rate
6. Response rate
7. Disease free survival rate
8. Local disease free survival rate
9. Quality of life

- Two patients excluded from the Full Analysis Set (one Immediate surgery, one CRT)
- Some data cleaning ongoing



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Baseline patient characteristics

| | | Immediate Surgery n=32 | GEMCAP n=20 | FOLFIRINOX n=20 | CRT n=16 |
|---|---|---|---|---|---|
| Age (yrs), median (IQR) | | 61 ( 54 , 66 ) | 64 ( 59 , 70 ) | 64 ( 63 , 70 ) | 66 ( 59 , 69 ) |
| Sex, n (%) | Female | 19 ( 59 % ) | 11 ( 55 % ) | 10 ( 50 % ) | 9 ( 56 % ) |
| | Male | 13 ( 41 % ) | 9 ( 45 % ) | 10 ( 50 % ) | 7 ( 44 % ) |
| Smoking Status, n (%) | Current | 7 ( 22 % ) | 4 ( 20 % ) | 2 ( 10 % ) | 3 ( 19 % ) |
| | Past | 11 ( 34 % ) | 8 ( 40 % ) | 3 ( 15 % ) | 8 ( 50 % ) |
| | Never | 14 ( 44 % ) | 8 ( 40 % ) | 15 ( 75 % ) | 5 ( 31 % ) |
| Diabetic Status, n (%) | No | 23 ( 72 % ) | 14 ( 70 % ) | 7 ( 35 % ) | 12 ( 75 % ) |
| | Type II | 5 ( 16 % ) | 4 ( 20 % ) | 8 ( 40 % ) | 3 ( 19 % ) |
| | Type II (on insulin) | 4 ( 12 % ) | 2 ( 10 % ) | 5 ( 25 % ) | 1 ( 6 % ) |
| WHO PS, n (%) | 0 | 16 ( 50 % ) | 7 ( 35 % ) | 8 ( 40 % ) | 9 ( 56 % ) |
| | 1 | 16 ( 50 % ) | 13 ( 65 % ) | 12 ( 60 % ) | 7 ( 44 % ) |
| CA19-9 (kU/L), median (IQR) | | 859 ( 200 , 1847 ) | 493 ( 181 , 1298 ) | 659 ( 130 , 1366 ) | 322 ( 67 , 717 ) |
| | No. Unknown | 2 | 1 | 2 | 0 |



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Resection details: resected patients n=52

| | | Immediate Surgery n=21 | GEMCAP n=12 | FOLFIRINOX n=11 | CRT n=8 |
|---|---|---|---|---|---|
| Extent of resection, n(%) | Resection with extended lymphadenectomy | 5 ( 24 % ) | 5 ( 42 % ) | 1 ( 9 % ) | 2 ( 25 % ) |
| | Standard resection | 16 ( 76 % ) | 7 ( 58 % ) | 10 ( 91 % ) | 6 ( 75 % ) |
| Vein resection, n(%) | Yes | 14 ( 67 % ) | 6 ( 50 % ) | 6 ( 55 % ) | 6 ( 75 % ) |
| | No | 7 ( 33 % ) | 6 ( 50 % ) | 5 ( 45 % ) | 2 ( 25 % ) |
| R Status, n(%) | R0 | 3 ( 14 % ) | 2 ( 17 % ) | 2 ( 18 % ) | 3 ( 37 % ) |
| | R1 | 17 ( 81 % ) | 10 ( 83 % ) | 9 ( 82 % ) | 5 ( 63 % ) |
| | R2 | 1 ( 5 % ) | 0 ( 0 % ) | 0 ( 0 % ) | 0 ( 0 % ) |
| Adjuvant therapy, n(%) | Yes | 17 ( 81 % ) | 10 ( 83 % ) | 9 ( 82 % ) | 7 ( 87 % ) |
| | No | 4 ( 19 % ) | 2 ( 17 % ) | 2 ( 18 % ) | 1 ( 13 % ) |



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Tumour characteristics: resected patients n=52

| | | Immediate Surgery n=21 | GEMCAP n=12 | FOLFIRINOX n=11 | CRT n=8 |
|---|---|---|---|---|---|
| Tumour, n(%) | pT1 | 0 ( 0 % ) | 0 ( 0 % ) | 3 ( 27 % ) | 2 ( 25 % ) |
| | pT2 | 4 ( 19 % ) | 4 ( 33 % ) | 0 ( 0 % ) | 2 ( 25 % ) |
| | pT3 | 17 ( 81 % ) | 8 ( 67 % ) | 8 ( 73 % ) | 4 ( 50 % ) |
| Nodes, n(%) | Negative | 2 ( 10 % ) | 5 ( 42 % ) | 3 ( 27 % ) | 6 ( 75 % ) |
| | Positive | 19 ( 90 % ) | 7 ( 58 % ) | 8 ( 73 % ) | 2 ( 25 % ) |
| Grade, n(%) | Undifferentiated | 0 ( 0 % ) | 1 ( 8 % ) | 0 ( 0 % ) | 0 ( 0 % ) |
| | Poor | 5 ( 24 % ) | 1 ( 9 % ) | 4 ( 36 % ) | 2 ( 25 % ) |
| | Moderate | 15 ( 71 % ) | 4 ( 33 % ) | 6 ( 55 % ) | 2 ( 25 % ) |
| | Well | 0 ( 0 % ) | 2 ( 17 % ) | 1 ( 9 % ) | 1 ( 13 % ) |
| | Not reported | 0 ( 0 % ) | 4 ( 33 % ) | 0 ( 0 % ) | 3 ( 37 % ) |
| | Unknown | 1 ( 5 % ) | 0 ( 0 % ) | 0 ( 0 % ) | 0 ( 0 % ) |
| Maximum Tumour Dimension (mm), median (IQR) | | 36 ( 32 , 45 ) | 30 ( 30 , 42 ) | 30 ( 22 , 35 ) | 32 ( 22 , 43 ) |



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Primary outcome - resection rate (R0 + R1)

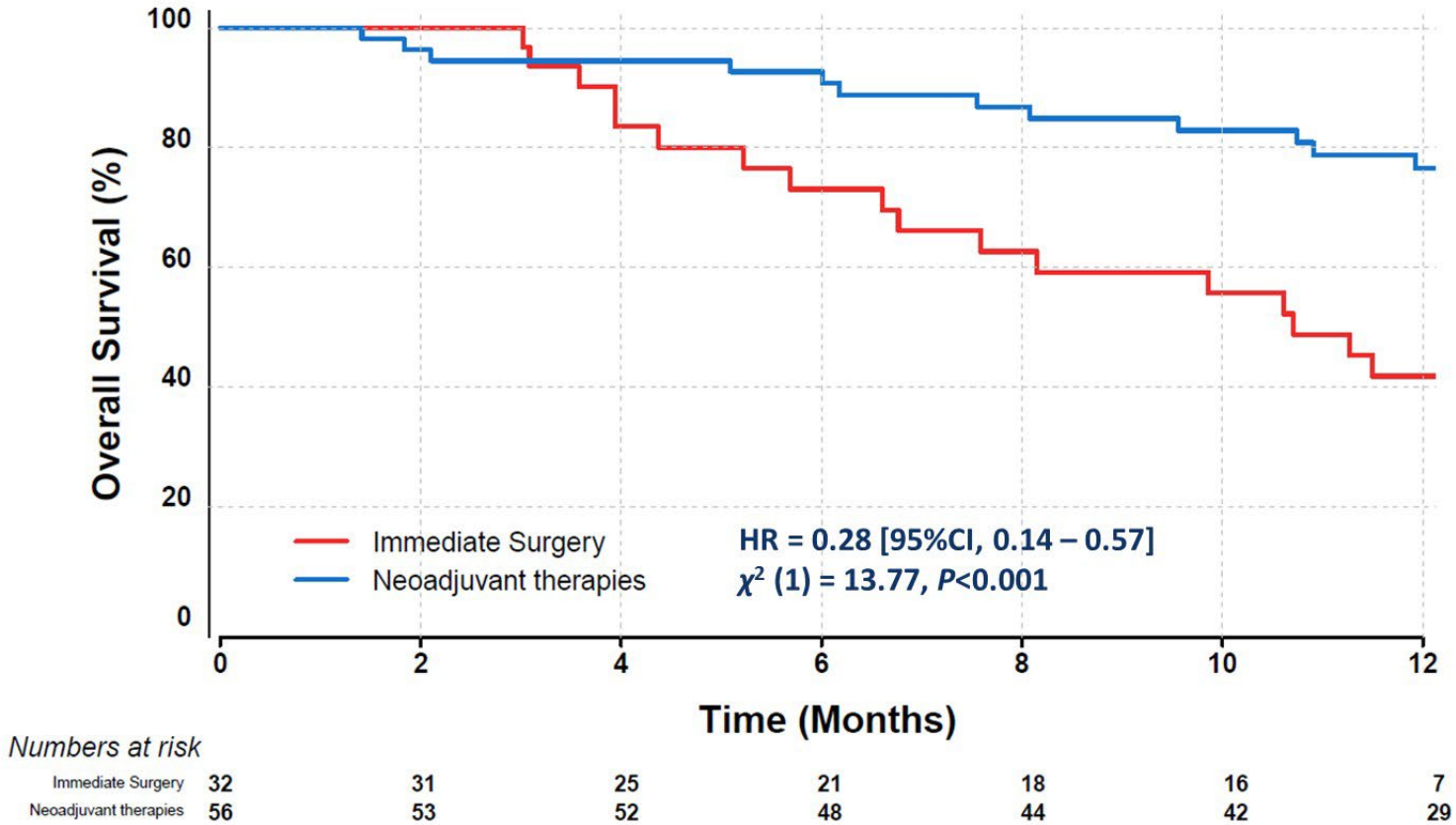
| | No of resections | No of patients | Rate* (95% CI) | P-value |
|---|---|---|---|---|
| Immediate Surgery | 20 | 32 | 62% ( 44% , 79 %) | 0.668 |
| Neoadjuvant treatment | 31 | 56 | 55% ( 41% , 69% ) | |
| Overall | 51 | 88 | 58% ( 47% , 68% ) | |

*Defined as R0 + R1 resections in patients included in the Full Analysis Set



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Secondary outcomes - overall survival (I)



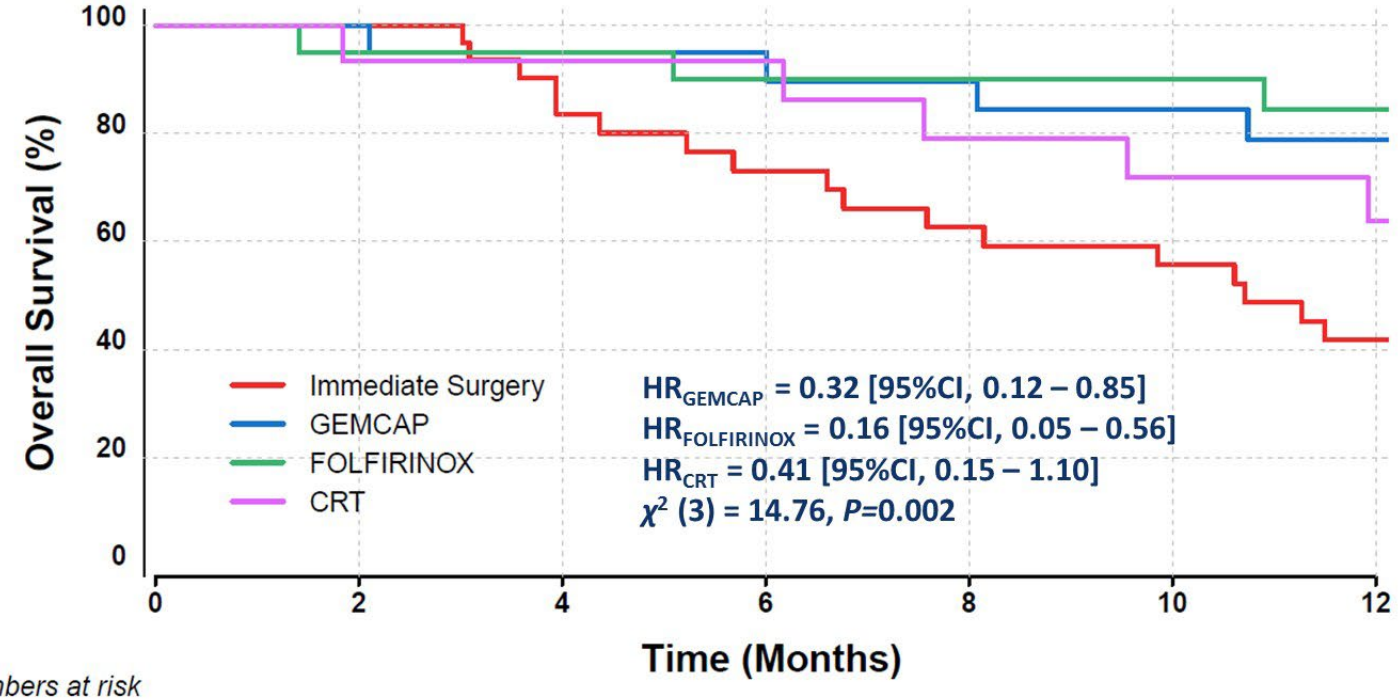

**12-months survival estimate (95% CI)**

| | |
|---|---|
| Immediate Surgery | 42% ( 27% , 64% ) |
| Neoadjuvant therapy | 77% ( 66% , 89% ) |



Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# Secondary outcomes - overall survival (II)




*Numbers at risk*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Immediate Surgery | 32 | 31 | 25 | 21 | 18 | 16 | 7 |
| GEMCAP | 20 | 20 | 19 | 18 | 17 | 16 | 7 |
| FOLFIRINOX | 20 | 19 | 19 | 17 | 16 | 16 | 14 |
| CRT | 16 | 14 | 14 | 13 | 11 | 10 | 8 |

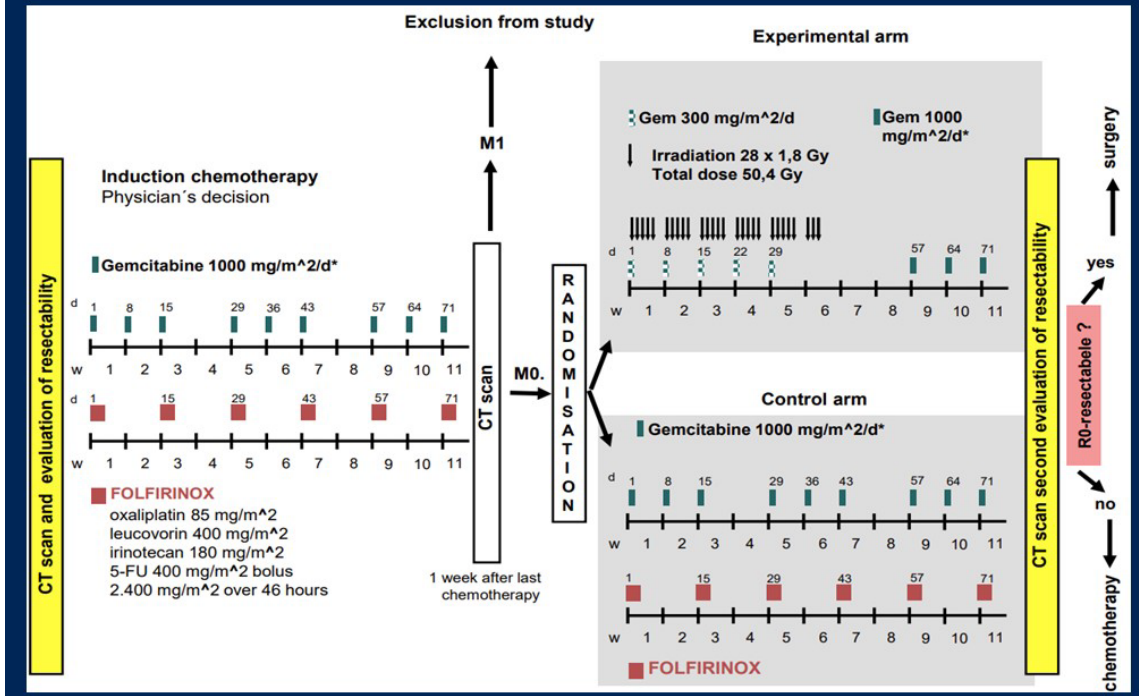
**12-months survival estimate (95% CI)**

| | |
|---|---|
| Immediate Surgery | 42% ( 27% , 64% ) |
| GEMCAP | 79% ( 62% , 100% ) |
| FOLFIRINOX | 84% ( 70% , 100% ) |
| CRT | 64% ( 43% , 95% ) |

Ghaneh, Palmer, Cicconi et. al, Lancet Gastroenterology Hepatology, 2023

# CONKO-007 Trial – Chemoradiotherapy versus Chemotherapy in Patients with LAPC

## Study design




**Primary Endpoint:**

- R0 Resection rate

**Secondary endpoints:**

- Overall survival; DFS
- Rate of resections
- Survival following resection

**Statistical considerations:**

- First calculation: primary endpoint was overall survival with 830 pts
- Following interim analysis: due to insufficient recruitment primary endpoint was changed to R0 resection with 525 pts
- Evaluation according to ITT
- Median Follow-up: 55.13 months (CI: 27.40 - 80.95)

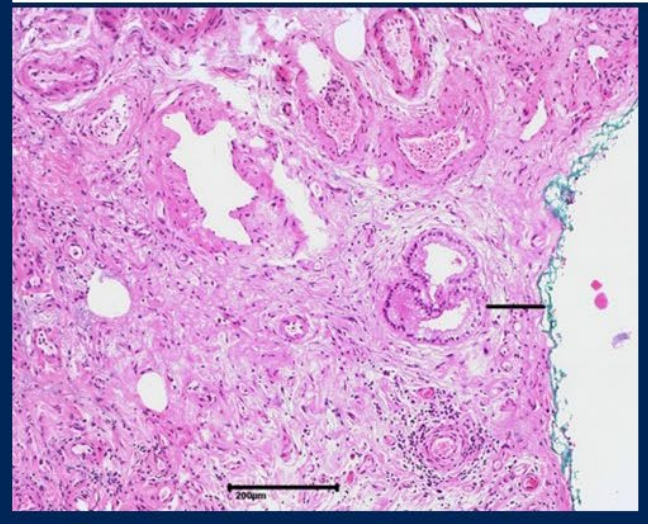
Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

## Resection Data I:
## compared to all patients with resection (60/62)

| | CT | CT+CRT | p-value |
|---|---|---|---|
| Resection performed, No. | 60 | 62 | |
| pCR, No. (%) | 1 (2) | 11 (18) | 0.0043 |
| | | | |
| R0 resection, No. (%) | 30 (50) | 43 (69) | 0.0418 |
| R1 resection, No. (%) | 16 (27) | 5 (8) | 0.0081 |
| R2, Rx resection, No. (%) | 14 (23) | 14 (23) | 1.0000 |
| | | | |
| CRM negative, No. (%) | 15 (25) | 29 (47) | 0.0147 |
| CRM positive, No. (%) | 27 (45) | 11 (18) | 0.0016 |
| CRM missing data, No. (%) | 4 (7) | 8 (13) | |
| | | | |
| Deceased within 30 days after resection, No. (%) | 5 (8) | 4 (6) | 0.7413 |

## definition of CRM status

| | | |
|---|---|---|
| CRM+ | 0 (tumor in the CRM) | R1 |
| | ≤ 1mm | R0 narrow |
| CRM- | > 1 mm | R0 wide |

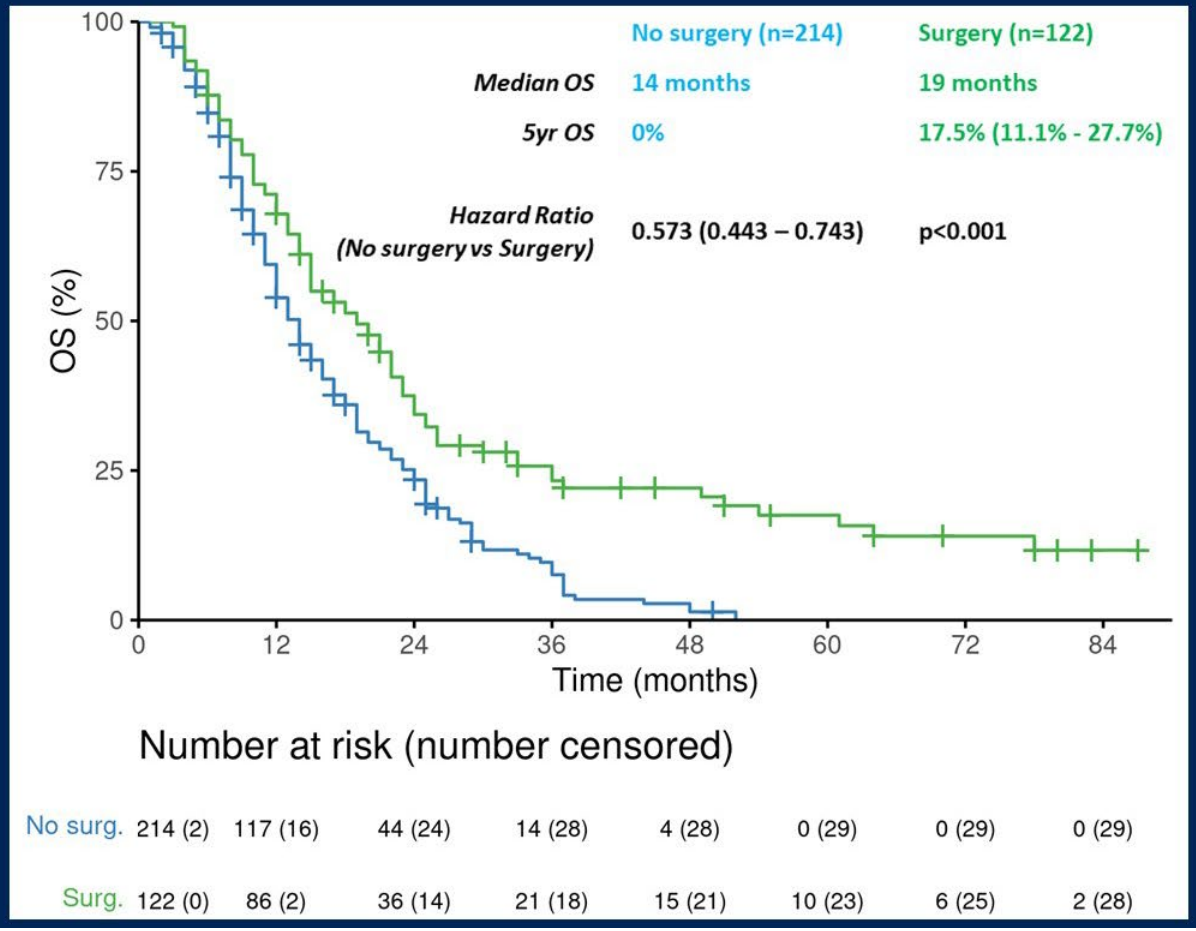


R0 narrow, CRM +

kindly provided by Prof. Tannapfel, Bochum



Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

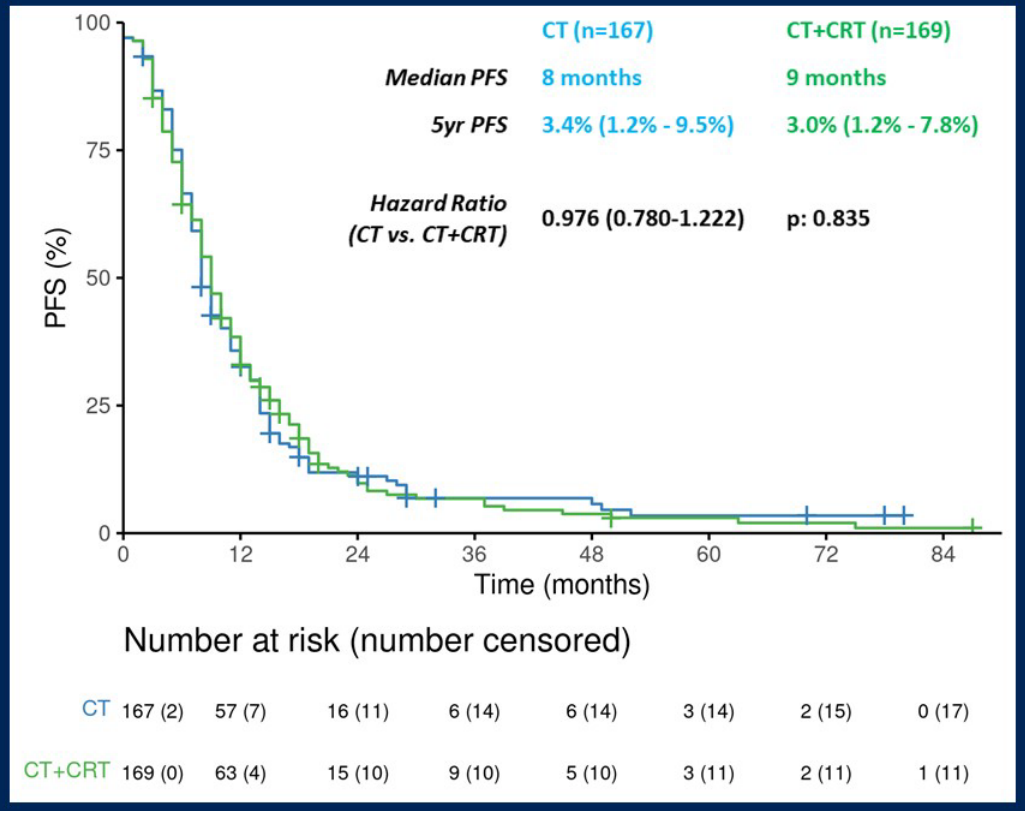



**Overall survival of all 336 randomized patients with/without surgery (T=0 date of randomization)**

Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

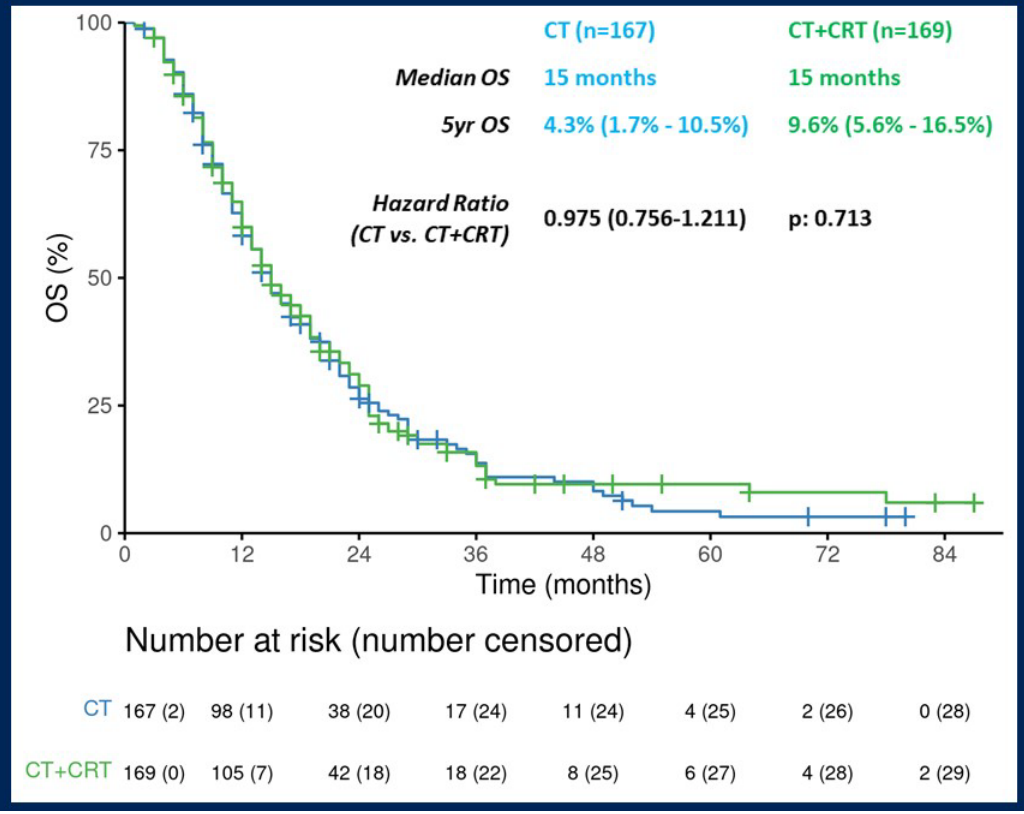
## PFS CT versus CRT

(randomized pts; T=0 date of randomization)




## Overall Survival CT versus CRT

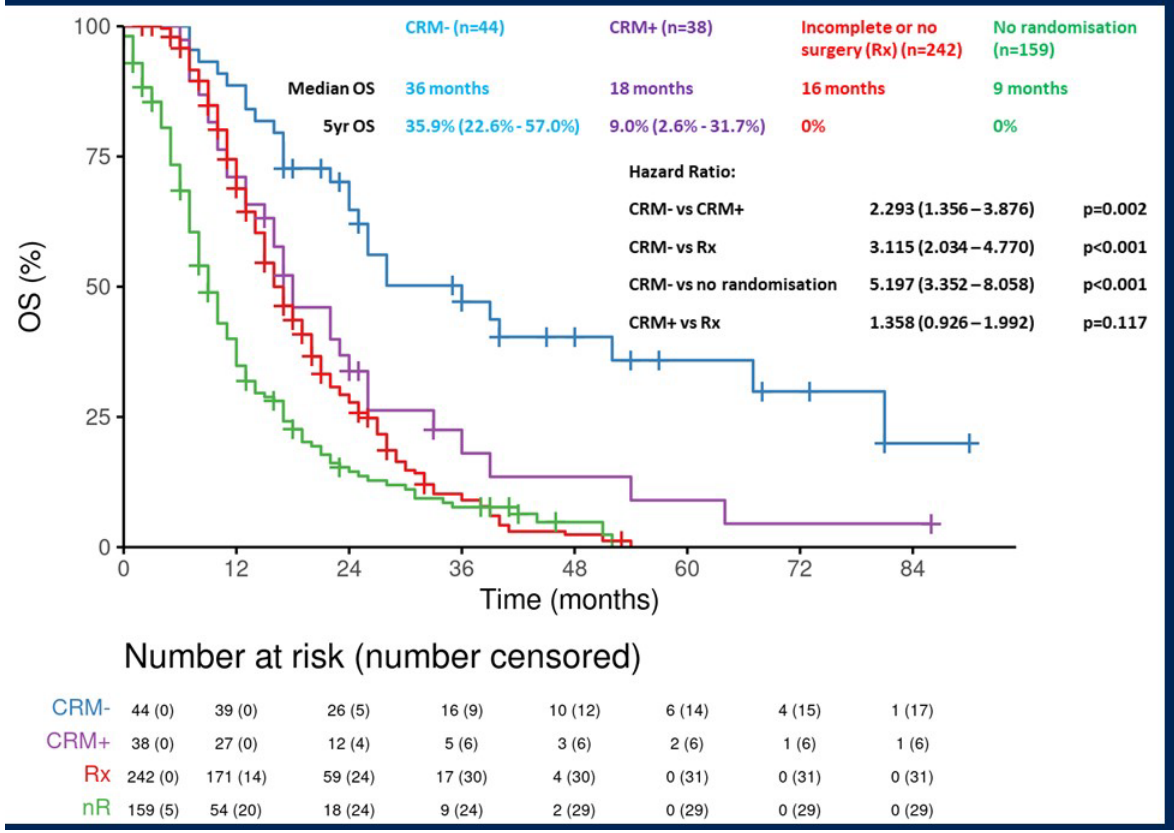
(randomized pts; T=0 date of randomization)



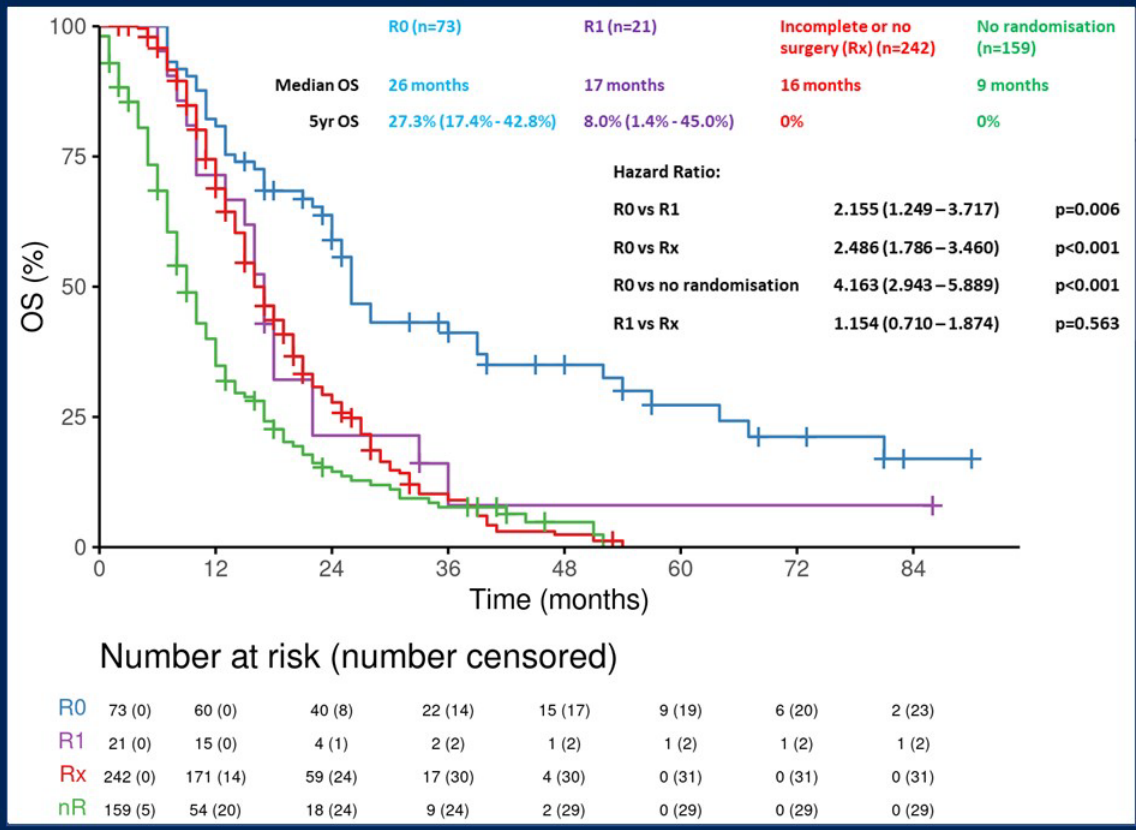

Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

## Overall survival (OS) divided by resection status (T=0: date of signed ICF)

### CRM - versus CRM + resection status

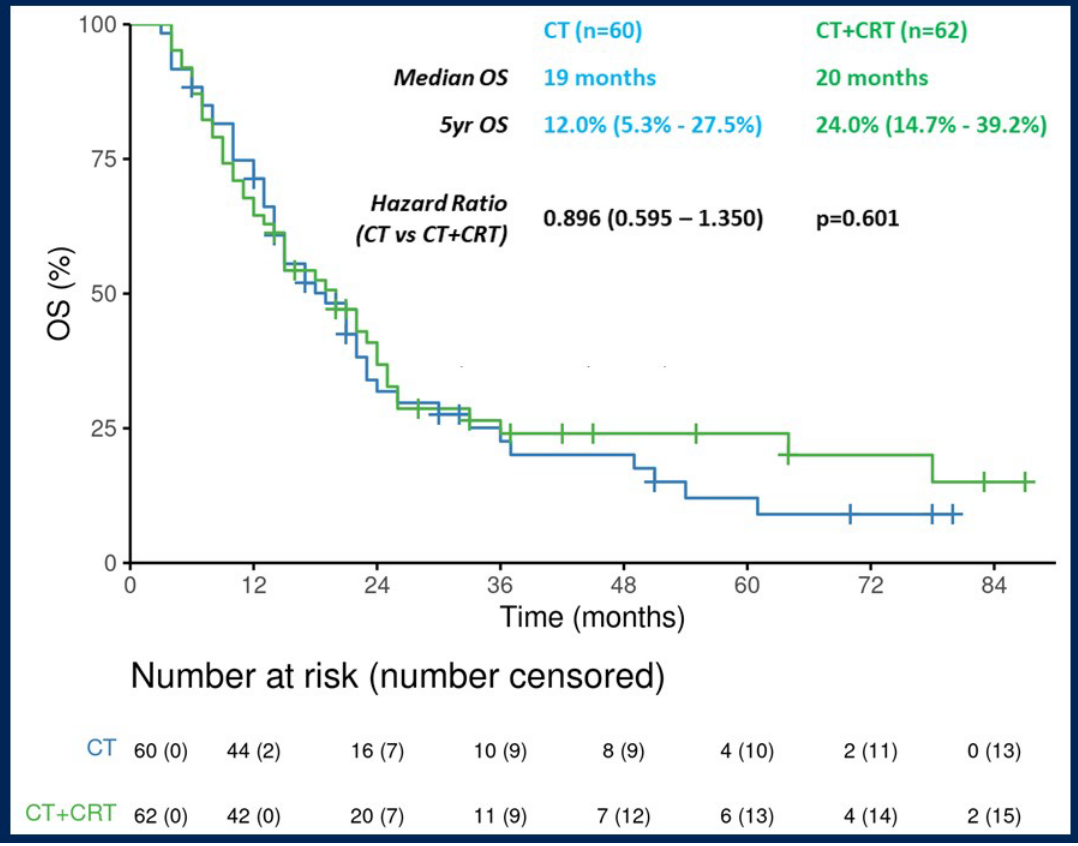



### R0 versus R1 resection status

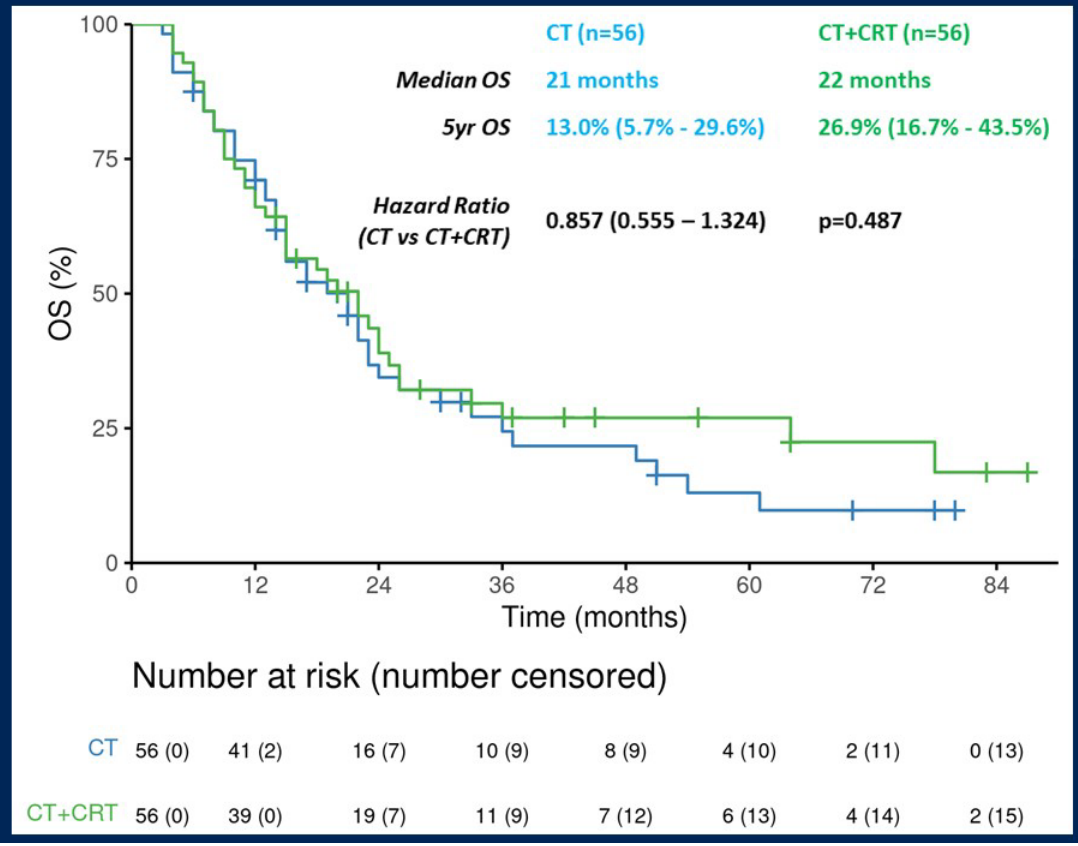



Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

**Subgroup-analysis of all surgically treated patients (N = 122)**
**Overall survival in randomized patients with surgery comparing CT (N = 60) and CTR (N = 62)**

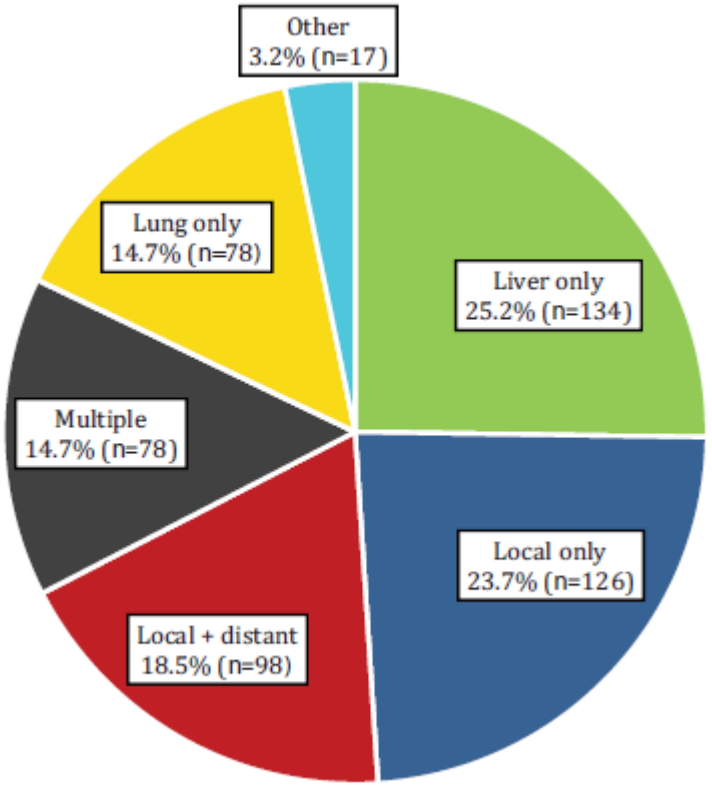



**Subgroup analysis of all surgical patients treated with FOLFIRINOX (N = 112)**
**Overall survival in randomized patients with surgery comparing CT (N = 56) versus CRT (N = 56)**

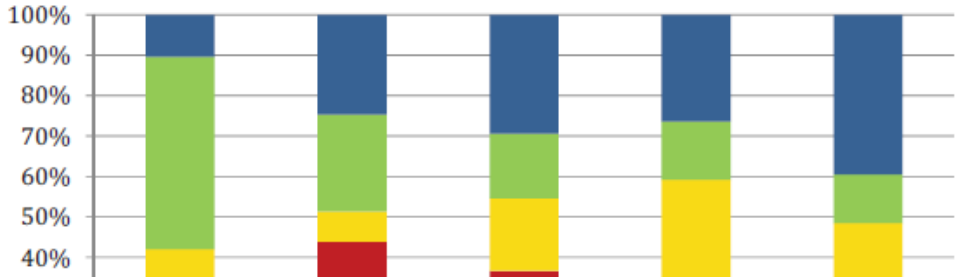



Fietkau, Ghadimi, Grutzmann et. al, ASCO, 2022

# Recurrence patterns after surgery




A



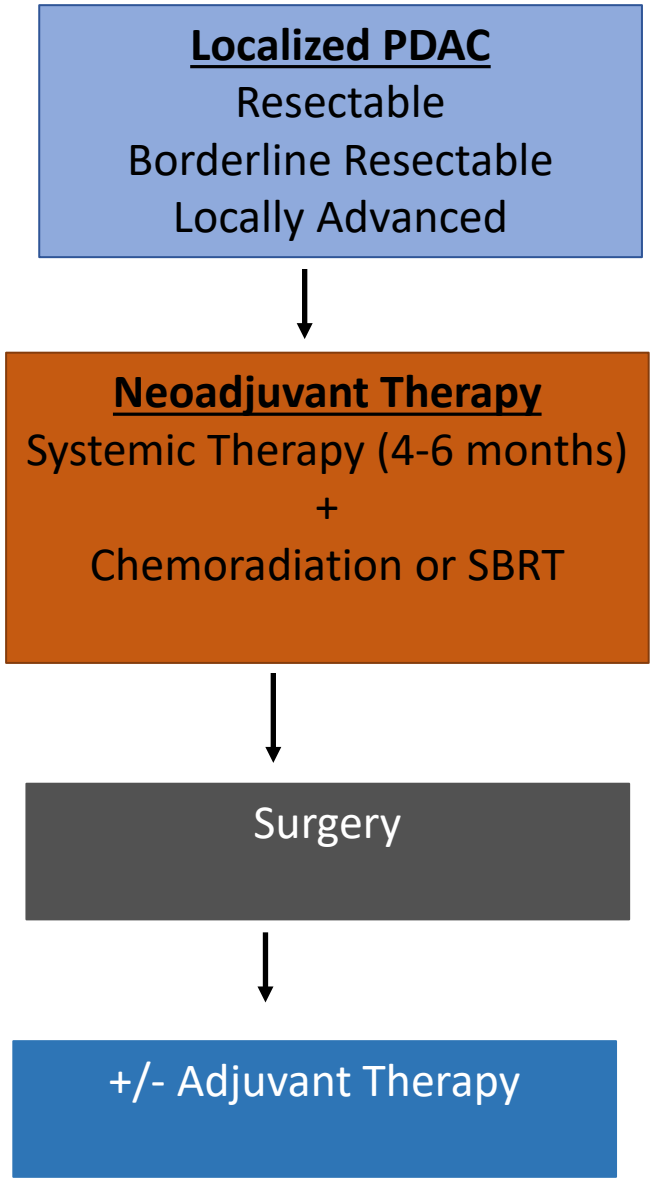

| | 0-6 months (n=126) | 6-12 months (n=146) | 12-24 months (n=150) | 24-48 months (n=76) | >48 months (n=33) |
|---|---|---|---|---|---|
| Local only | 10.3% | 24.7% | 29.3% | 26.3% | 39.4% |
| Liver only | 47.6% | 24.0% | 16.0% | 14.5% | 12.1% |
| Lung only | 7.9% | 7.5% | 18.0% | 27.6% | 27.3% |
| Local + distant | 20.6% | 24.7% | 15.3% | 14.5% | 6.1% |
| Multiple | 11.1% | 18.5% | 16.0% | 14.5% | 6.1% |
| Other | 2.4% | 0.7% | 5.3% | 2.6% | 9.1% |

Groot, Rezaee, Wu et al, Annals of Surgery, 2018

# Summary

- Local Recurrence alone (in the absence of systemic recurrence) was a rare occurrence in localized pancreas cancer due to the relatively modest mOS of patients treated with curative intent surgery
- As the mOS of patients with localized pancreatic cancer continues to improve, there is an increased role for local control in patients treated with systemic therapy + curative intent surgery
- In patients with inoperable pancreas cancer, RT can be used to consolidate local control after careful assessment of biology and multidisciplinary discussion
- The optimal modality and dose of RT in specific situations – operable vs inoperable pancreas cancer – needs to be prospectively validated

# Treatment Overview

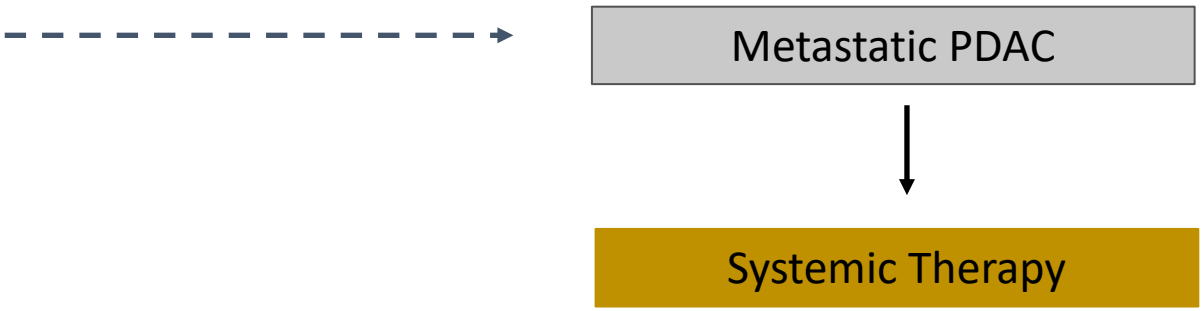



What is the Optimal Neoadjuvant Systemic Therapy?

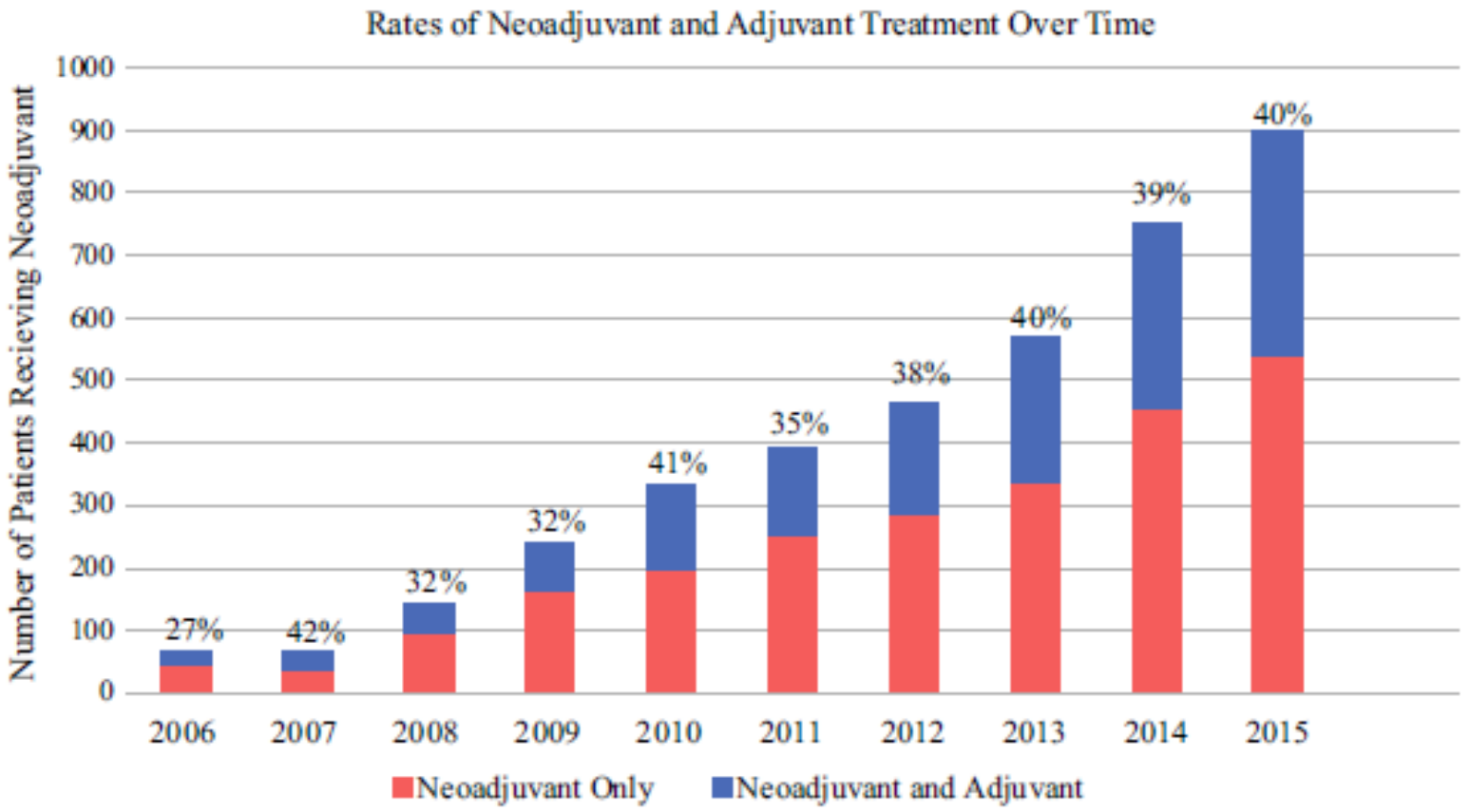
Response Assessment to Neoadjuvant Therapy

Role of Radiation Therapy in the Treatment of BRPC and LAPC

**Adjuvant Therapy after Neoadjuvant Therapy**



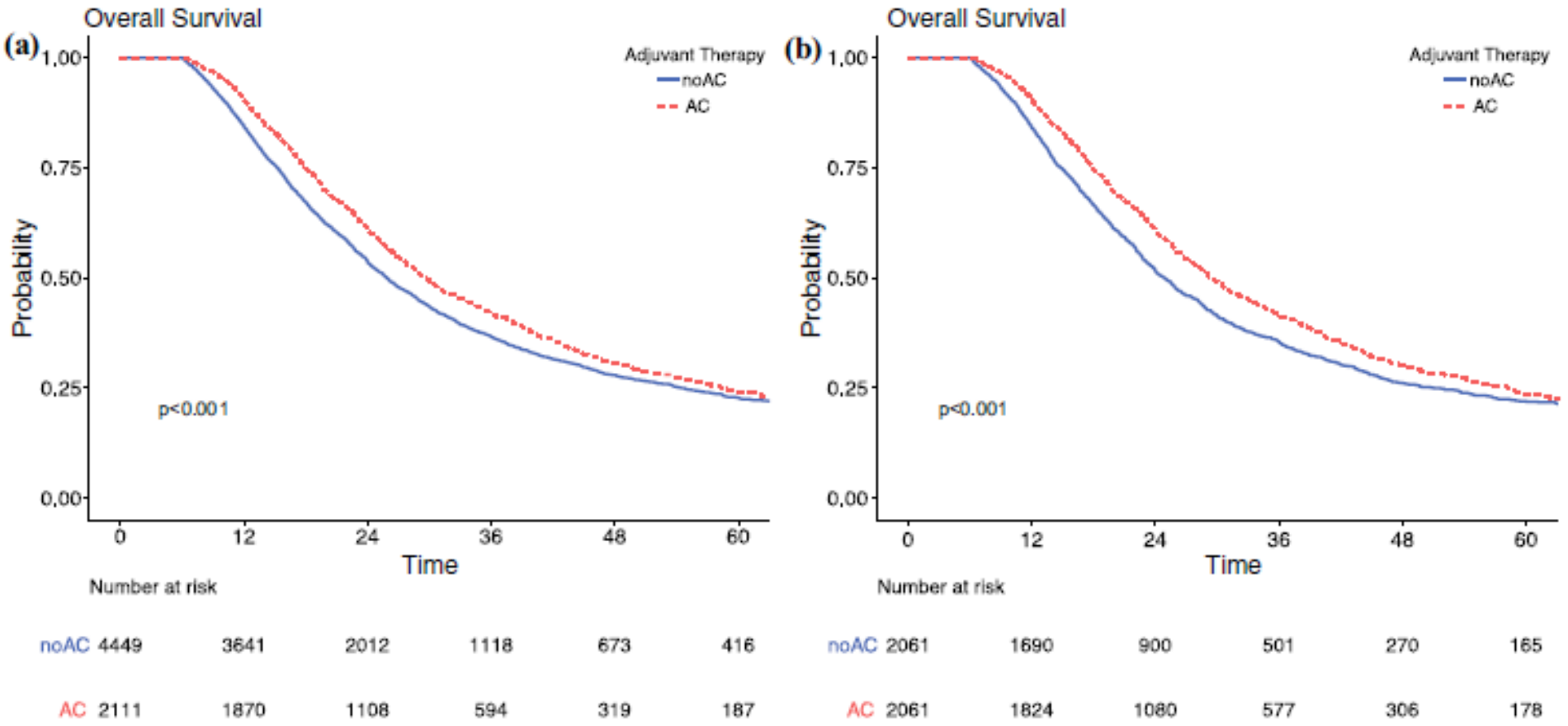
# Adjuvant Chemotherapy after Neoadjuvant Therapy




Olecki, Stahl. Torres et. al, Annals of Surgical Oncology, 2021

# Adjuvant Chemotherapy after Neoadjuvant Therapy – NCDB cohort

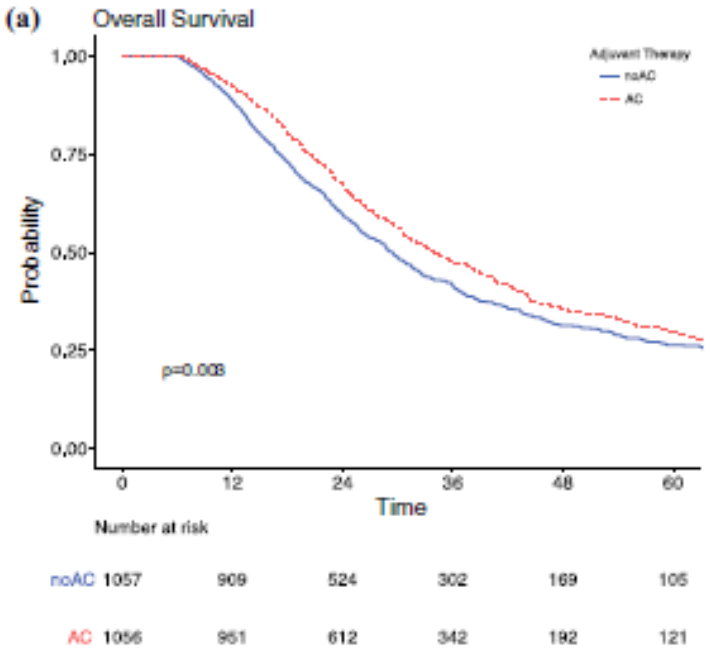
N = 6560
AC = 2111
No AC = 4449



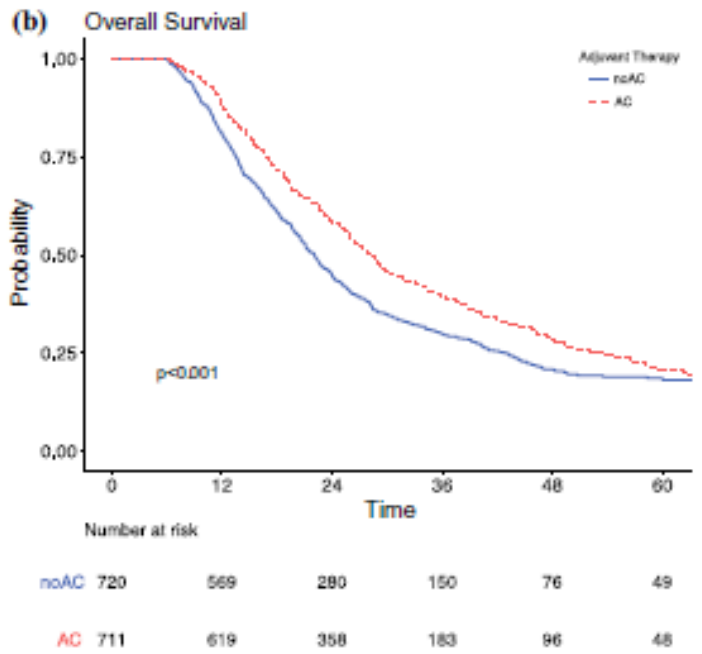

Kamarajah, White, Naffoujeh et. al, Annals of Surgical Oncology, 2021

# Adjuvant Chemotherapy after Neoadjuvant Therapy - Matched NCDB cohort

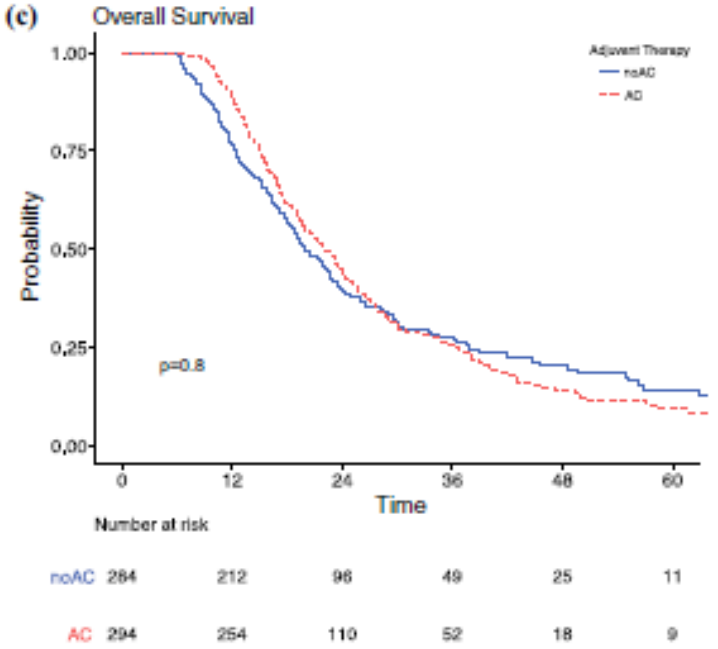
AC =2061, No AC =2061




N0




N1




N2+

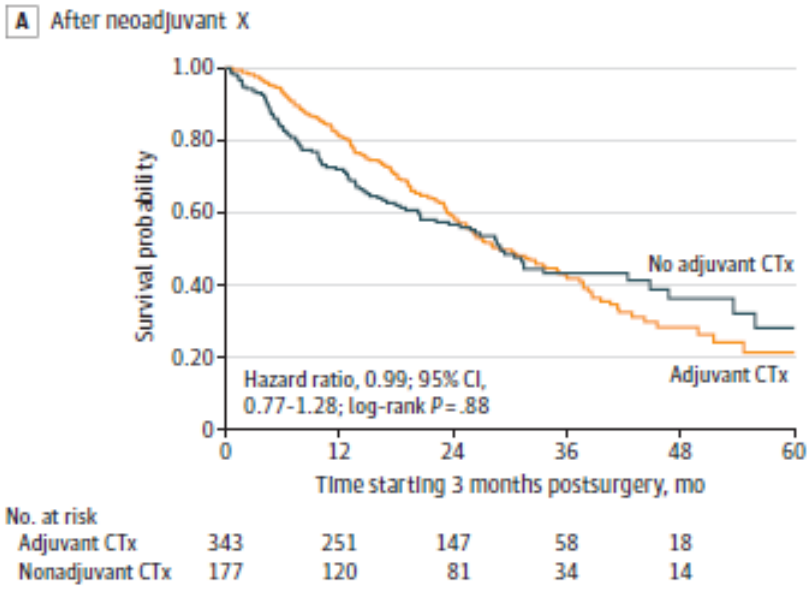
Kamarajah, White, Naffoujeh et. al, Annals of Surgical Oncology, 2021

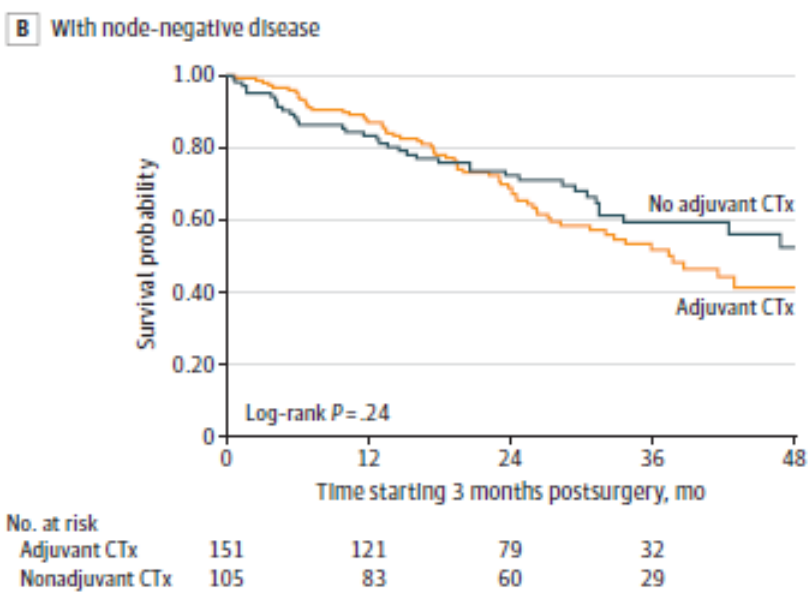


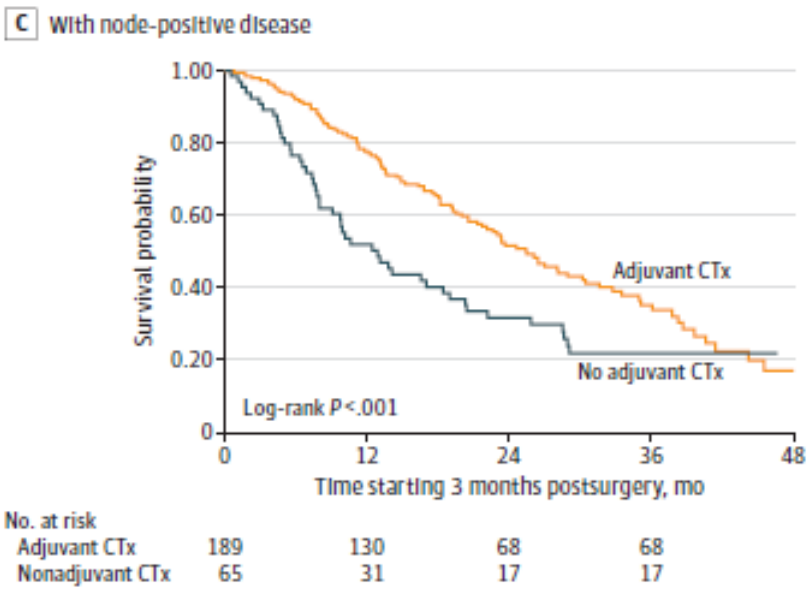
Froedtert & Medical College of Wisconsin

# Adjuvant Chemotherapy after Neoadjuvant Therapy

N =520; RP, BRPC, and LAPC; at least 2 cycles of neoadjuvant FOLFIRINOX




Roessel, van Veldhuisen, Klompmaker et. al, JAMA Oncology, 2020



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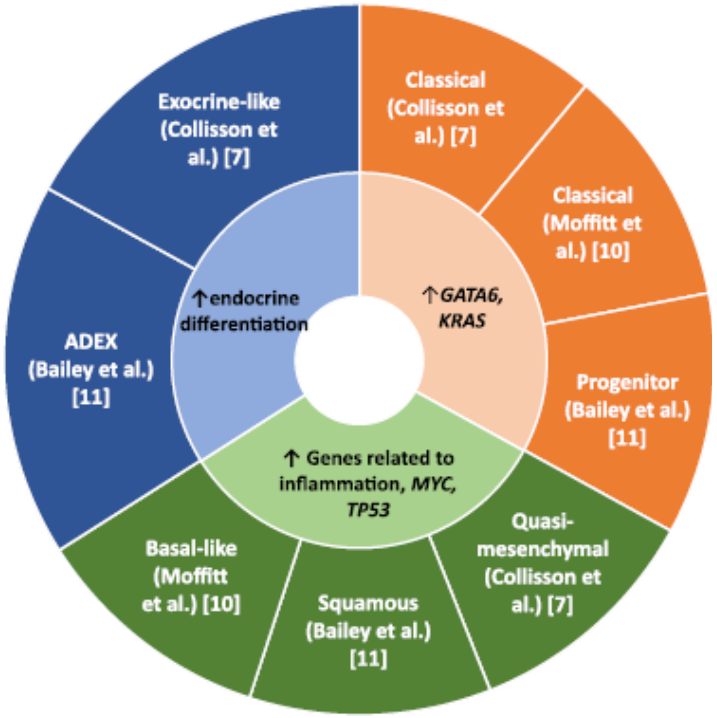
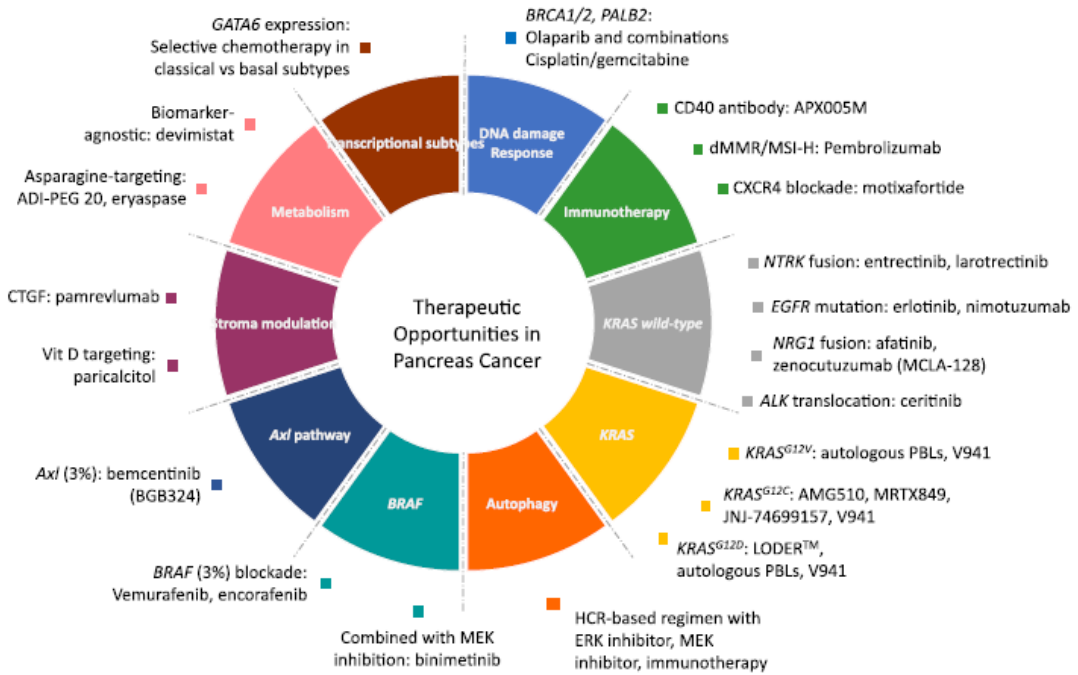
# Treatment of Pancreatic Cancer in the Precision Medicine Era




| Alteration | Rate | Detection |
|---|---|---|
| ***BRCA1/2, PALB2* [18, 19]** | 5-9% | Multigene NGS panel, i.e. BRAC-Analysis CDx test |
| ***NTRK* fusion [69]** | 0.34% | - IHC with pan-TREK rabbit mAb<br>- DNA-/RNA-based NGS |
| ***NRG1* fusion [81]** | 0.5% | Multiplex PCR for targeted RNA sequencing |
| ***ALK* translocation [85]** | 0.16% | - IHC with rabbit mAb<br>- NGS |
| **$KRAS^{G12D}$ [8]** | 40% | NGS |
| **$KRAS^{G12V}$ [8]** | 30% | NGS |
| **$KRAS^{G12C}$ [8]** | 1% | NGS |
| ***BRAF* [8]** | 3% | NGS |
| **dMMR [43]** | 1.5% | IHC stain for mismatch repair enzymes |
| **MSI-H [43]** | 0.8% | - PCR<br>- MSIsensor analysis |
| ***Axl* [100]** | 3.1% | - ELISA<br>- NGS |

Zheng-Lin and O'Reilly, Seminars in Oncology, 2021

# Summary

- Efforts must be maximized to eliminate micro-metastatic disease
- Monitoring/identifying minimal residual disease remains a challenge
- The physiologic impact of curative intent, multi-modality therapy necessitates pragmatic adjuvant therapy strategies
- Clinical trial participation must be maximized in the peri-operative setting to increase cure rates