# Neoadjuvant Versus Adjuvant Therapy for Pancreatic Adenocarcinoma

## South Florida GI Cancer Symposium – 2025


Gulam Abbas Manji, MD PhD

Associate Professor of Medicine

Section Chief Gastrointestinal Medical Oncology, Division of Hematology and Oncology

Co-Director, Pancreas Center

Co-Leader Precision Oncology and Systems Biology, Herbert Irving Comprehensive Cancer Center

# Objectives

- Epidemiology
- Clinical Staging
- Treatment of Pancreas Cancer

  Resectable Disease

  Borderline Resectable

# Epidemiology – 2024 Estimates

**Estimated New Cases**

| Male | | | Female | | |
|---|---|---|---|---|---|
| Prostate | 299,010 | 29% | Breast | 310,720 | 32% |
| Lung & bronchus | 116,310 | 11% | Lung & bronchus | 118,270 | 12% |
| Colon & rectum | 81,540 | 8% | Colon & rectum | 71,270 | 7% |
| Urinary bladder | 63,070 | 6% | Uterine corpus | 67,880 | 7% |
| Melanoma of the skin | 59,170 | 6% | Melanoma of the skin | 41,470 | 4% |
| Kidney & renal pelvis | 52,380 | 5% | Non-Hodgkin lymphoma | 36,030 | 4% |
| Non-Hodgkin lymphoma | 44,590 | 4% | Pancreas | 31,910 | 3% |
| Oral cavity & pharynx | 41,510 | 4% | Thyroid | 31,520 | 3% |
| Leukemia | 36,450 | 4% | Kidney & renal pelvis | 29,230 | 3% |
| 10 Pancreas | 34,530 | 3% | Leukemia | 26,320 | 3% |
| **All sites** | **1,029,080** | | **All sites** | **972,060** | |

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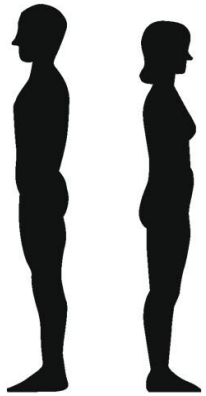

**Estimated Deaths**

| Male | | | Female | | |
|---|---|---|---|---|---|
| Lung & bronchus | 65,790 | 20% | Lung & bronchus | 59,280 | 21% |
| Prostate | 35,250 | 11% | Breast | 42,250 | 15% |
| Colon & rectum | 28,700 | 9% | Pancreas | 24,480 | 8% |
| 4 Pancreas | 27,270 | 8% | Colon & rectum | 24,310 | 8% |
| Liver & intrahepatic bile duct | 19,120 | 6% | Uterine corpus | 13,250 | 5% |
| Leukemia | 13,640 | 4% | Ovary | 12,740 | 4% |
| Esophagus | 12,880 | 4% | Liver & intrahepatic bile duct | 10,720 | 4% |
| Urinary bladder | 12,290 | 4% | Leukemia | 10,030 | 3% |
| Non-Hodgkin lymphoma | 11,780 | 4% | Non-Hodgkin lymphoma | 8,360 | 3% |
| Brain & other nervous system | 10,690 | 3% | Brain & other nervous system | 8,070 | 3% |
| **All sites** | **322,800** | | **All sites** | **288,920** | |

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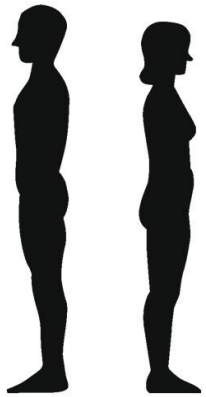
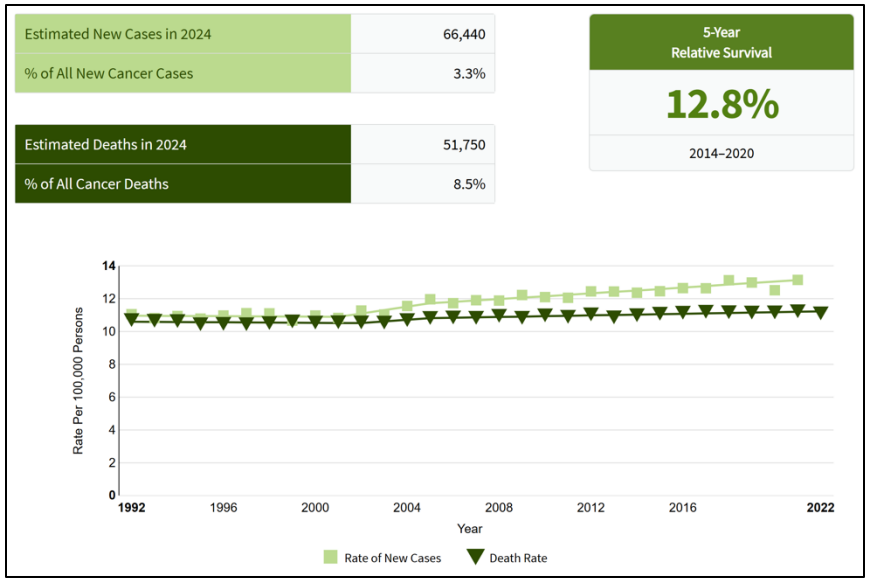
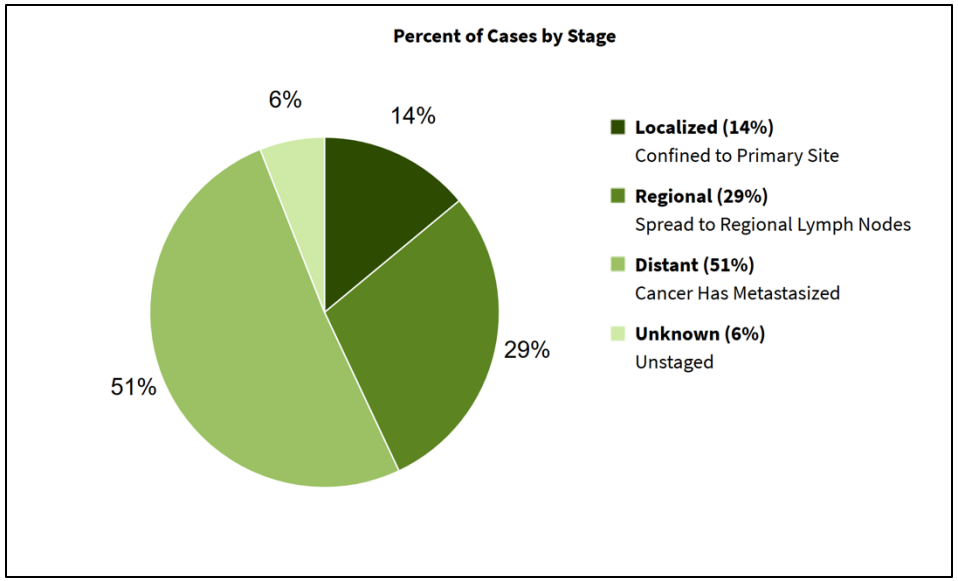
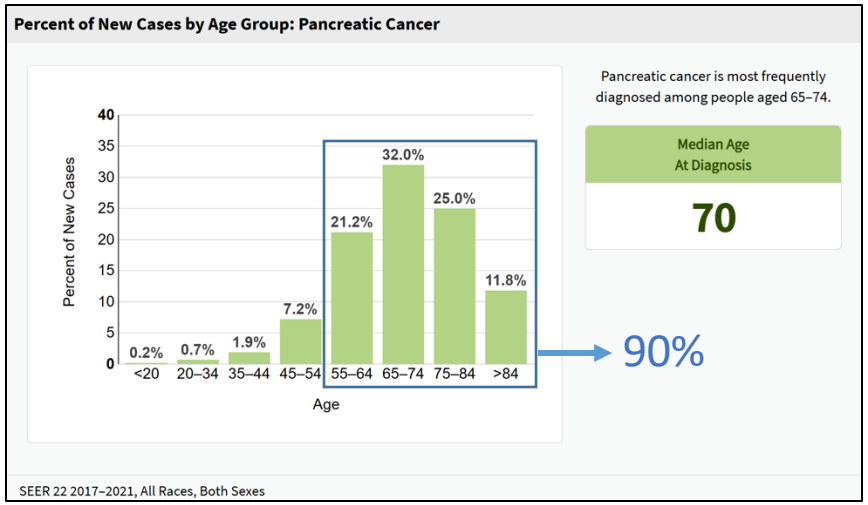


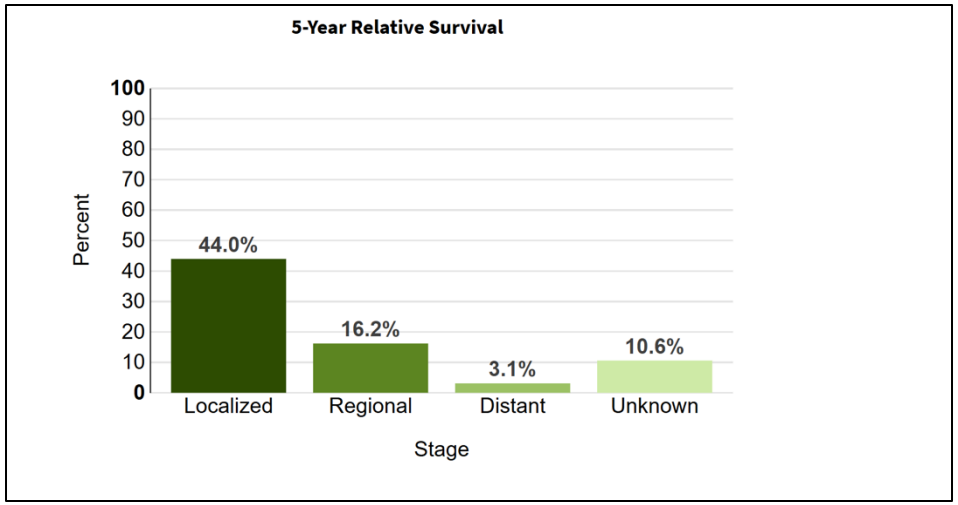
Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

# Epidemiology – SEER (2017 – 2021)



# Case Presentation

A 64 year-old man with no significant past medical history presents with 3 months of intermittent epigastric pain. He underwent EGD and found to have biopsy-confirmed H. pylori gastritis. Despite treatment, his pain increased and he presented to the Emergency Department for further evaluation.

ECOG Performance Status: 1

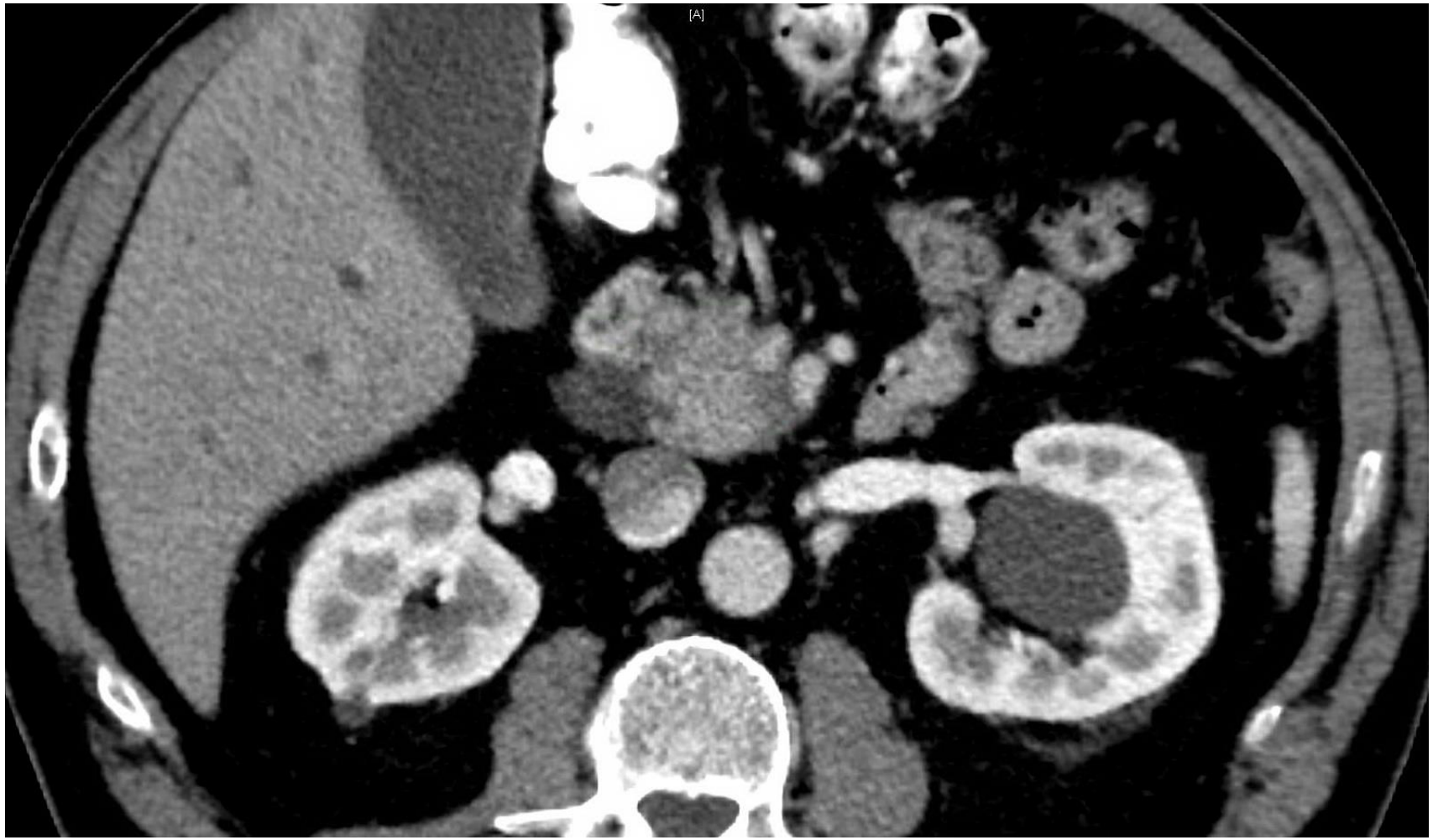
Laboratory Findings:

| | |
|---|---|
| Blood glucose | 753 mg/dL |
| Alkaline phosphatase | 137 IU/L |
| Bilirubin | 0.9 mg/dL |
| CA 19-9 | 459 U/mL |

Manji GA and Vollmer CM. ASCO Education. 2019.

# Case Presentation

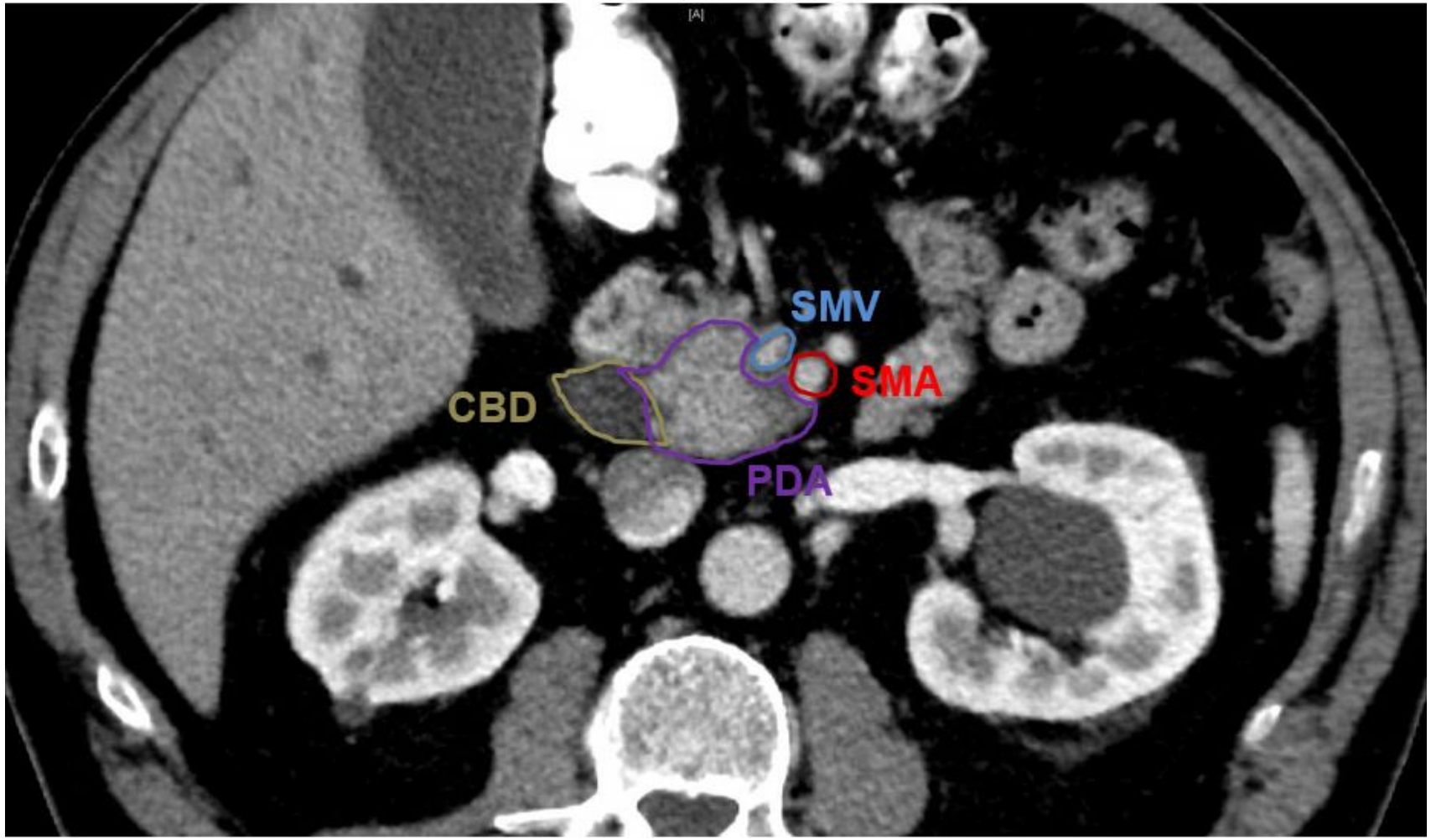
## Triple-Phase CT Scan




Manji GA and Vollmer CM. ASCO Education. 2019.

# Case Presentation

## Triple-Phase CT Scan




CBD – Common Bile Duct; PDA – Pancreatic Ductal Adenocarcinoma;
SMV – Superior Mesenteric Vein; SMA – Superior Mesenteric Artery

Manji GA and Vollmer CM. ASCO Education. 2019.

# Case Presentation

Would you recommend

A. Surgery

B. Systemic chemotherapy with mFOLFIRINOX

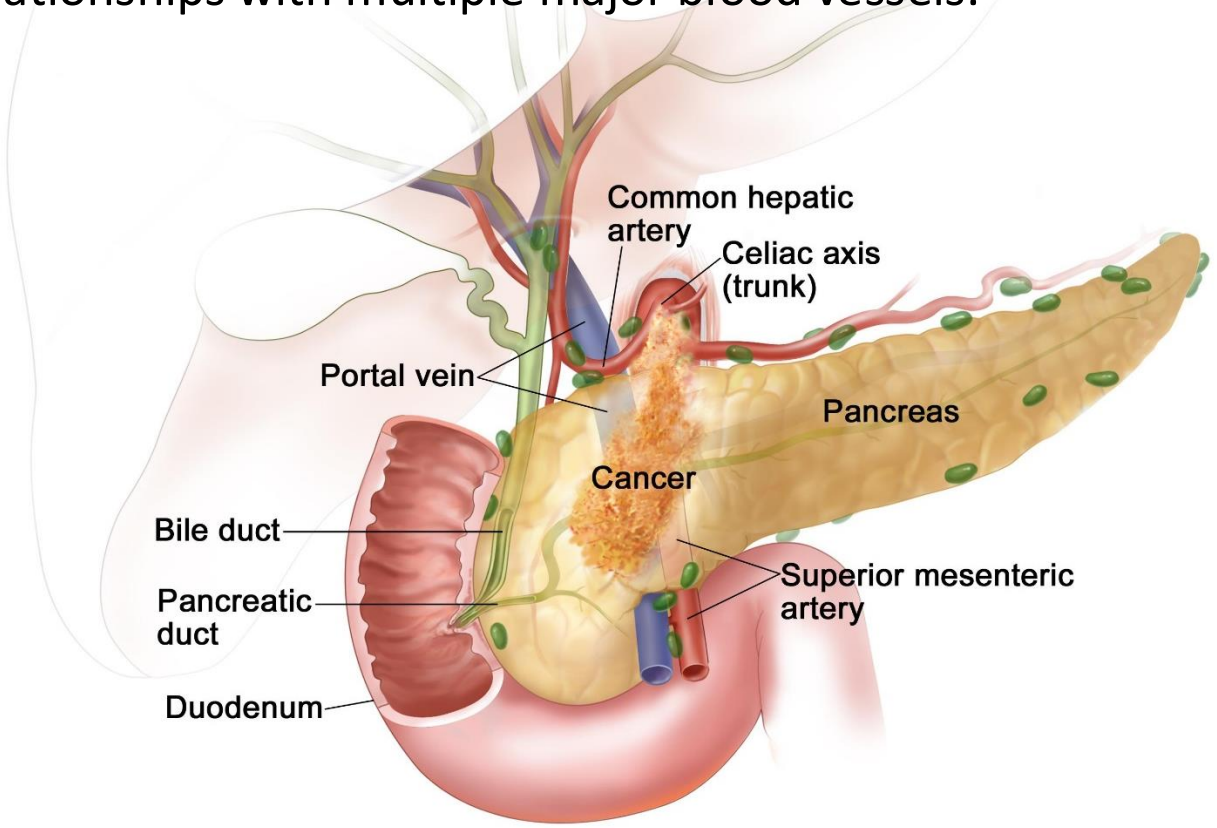
C. Chemo-radiotherapy or stereotactic body radiation therapy (SBRT)

D. Irreversible electroporation (IRE)/Nano-knife surgery

Manji GA and Vollmer CM. ASCO Education. 2019.

# Anatomy and Staging

Retroperitoneal organ that has close anatomic relationships with multiple major blood vessels.




**Unresectable**

- Distant metastases
- Arterial encasement (celiac trunk, superior mesenteric artery, or hepatic artery)
- Arterial involvement (celiac trunk, superior mesenteric artery, or hepatic artery)
- Venous encasement (portal or superior mesenteric vein)
- Venous involvement (portal or superior mesenteric vein)
- Attached to other organs
- No arterial or venous involvement

**Resectable**

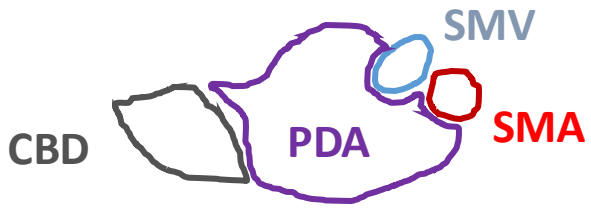
Locally Advanced

Borderline Resectable

Ryan DP et al., NEJM 2014;371:1039-1049
https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq#section/_139

Manji GA and Vollmer CM. ASCO Education. 2019.

# Case Presentation

| Resectability Status | Arterial | Venous |
|---|---|---|
| Resectable | • No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). | • No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity. |
| Borderline Resectable[b] | <u>Pancreatic head/uncinate process</u>:<br>• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.<br>• Solid tumor contact with the SMA of ≤180°<br>• Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning.<br><u>Pancreatic body/tail</u>:<br>• Solid tumor contact with the CA of ≤180°<br>• Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure (some panel members prefer these criteria to be in the locally advanced category). | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.<br>• Solid tumor contact with the inferior vena cava (IVC).<br>  |
| Locally Advanced[b,c] | <u>Head/uncinate process</u>:<br>• Solid tumor contact with SMA >180°<br>• Solid tumor contact with the CA >180°<br><u>Pancreatic body/tail</u>:<br>• Solid tumor contact of >180° with the SMA or CA<br>• Solid tumor contact with the CA and aortic involvement | • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |

NCCN National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2021**
**Pancreatic Adenocarcinoma**

Manji GA and Vollmer CM. ASCO Education. 2019.

# Case Presentation

Would you recommend

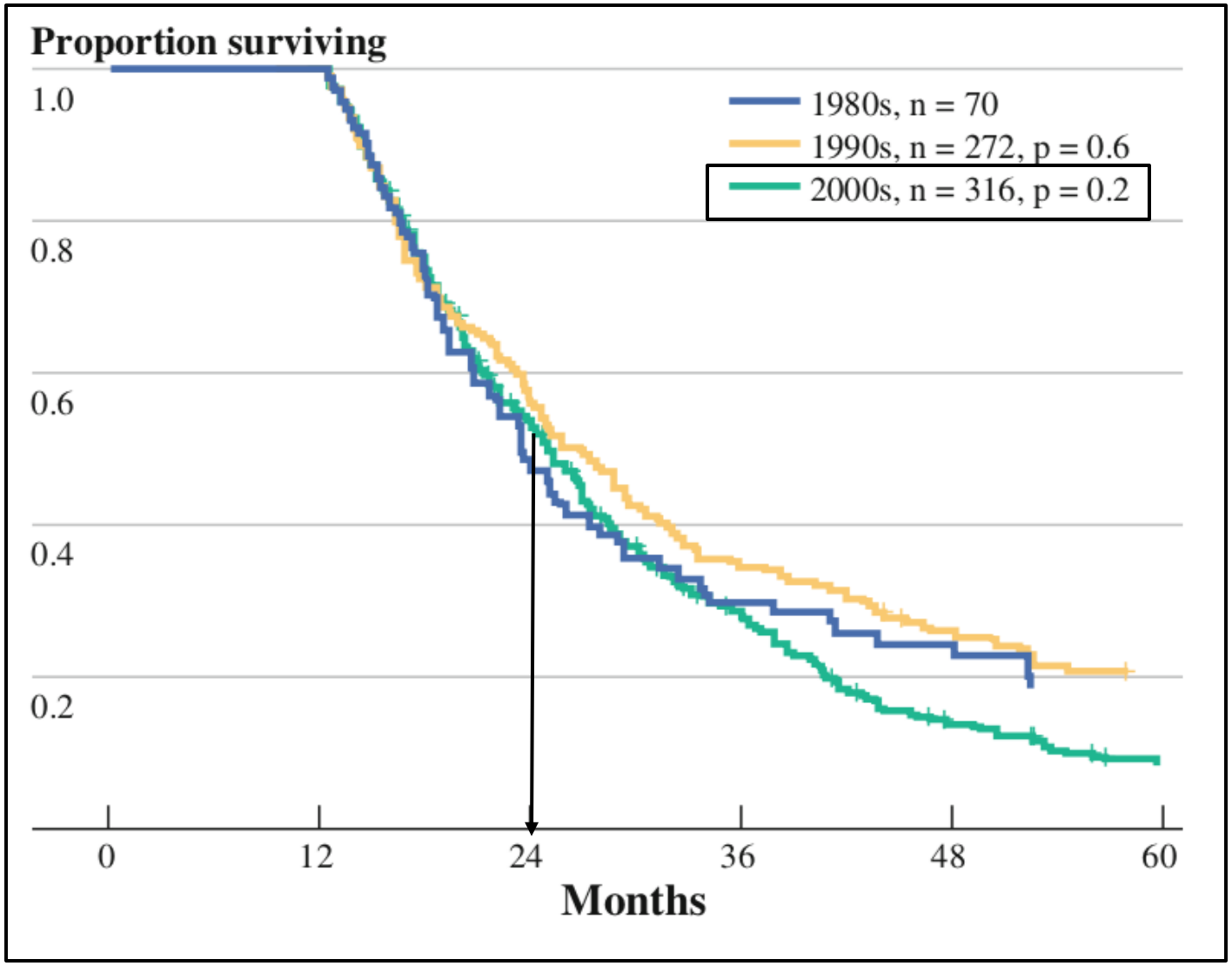
A. Surgery

B. Systemic chemotherapy with mFOLFIRINOX

C. Chemo-radiotherapy or stereotactic body radiation therapy (SBRT)

D. Irreversible electroporation (IRE)/Nano-knife surgery

# Outcomes – Upfront Resection with Time

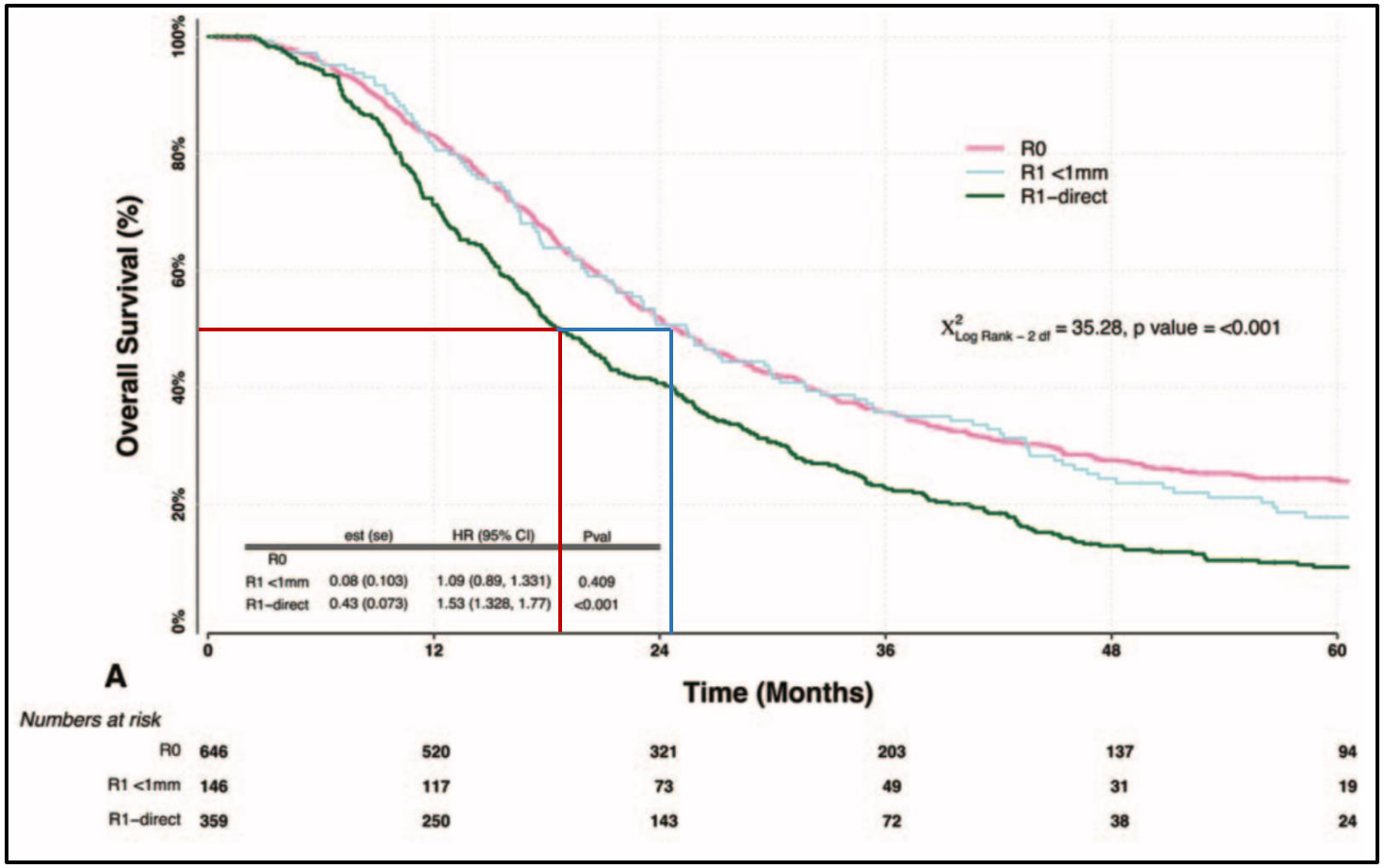





Winter JM et al. Ann Surg Oncol. 2012.

# Outcomes – Margin Status

## ESPAC-3: R0 vs R1

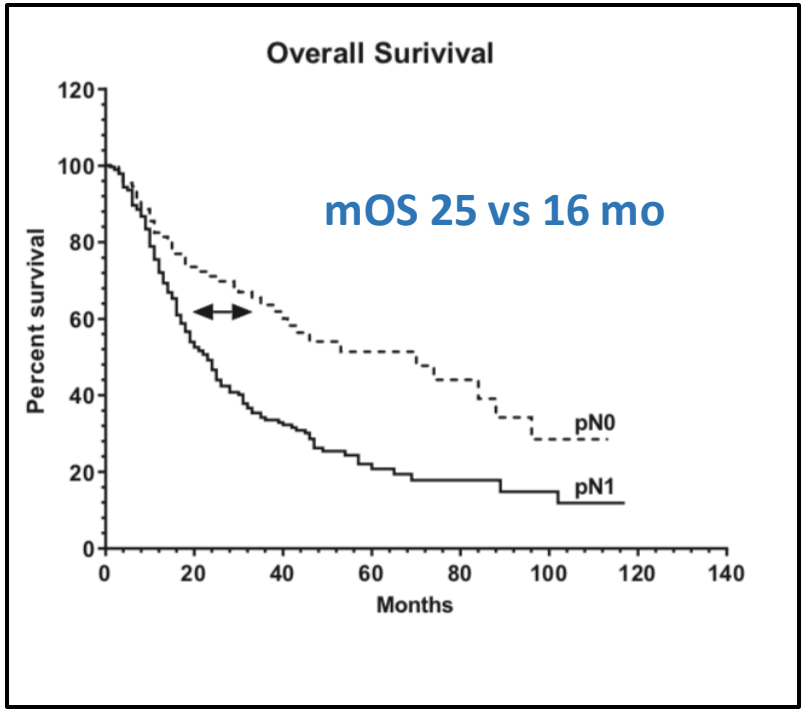





Ghaneh P et al. Ann Surg. 2019.

# Outcomes – Lymph Nodal Status

## Nodal Status

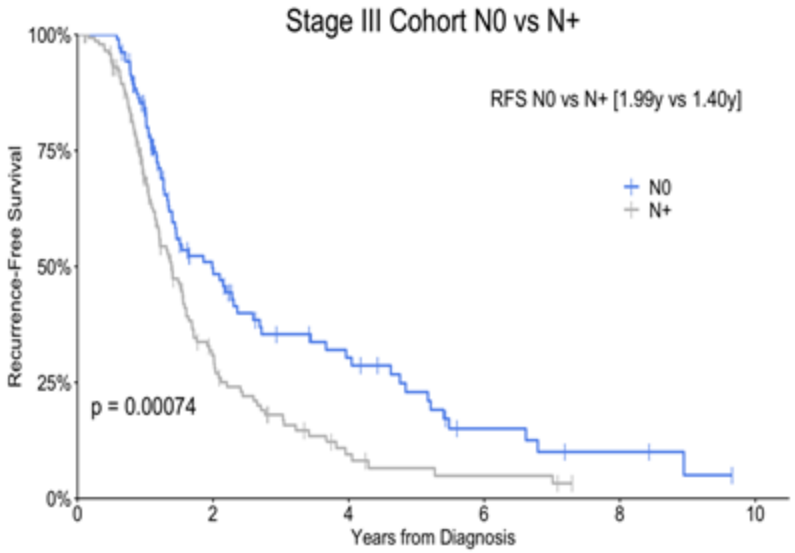


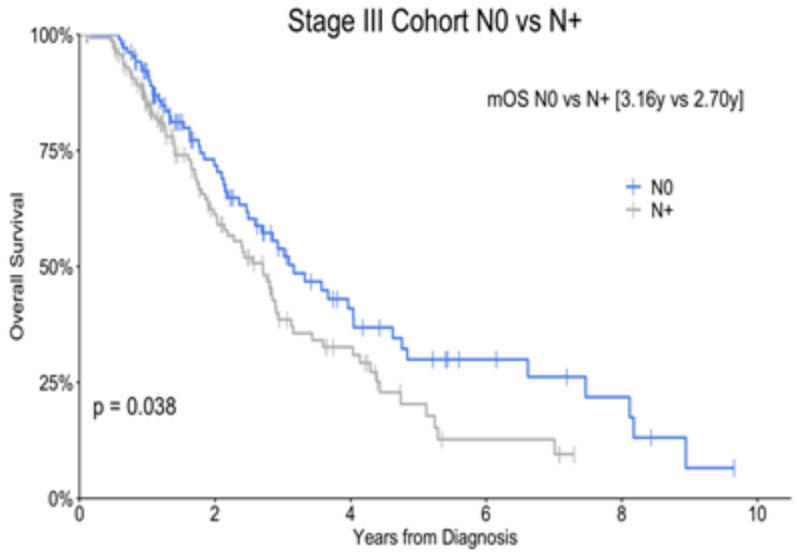

pN0 = 109 (CA 19-9: 65 U/mL, R1 31%, 72% adj.)

pN1 = 285 (CA 19-9: 140 U/mL, R1 59%, 75% adj.)

Honselmann KC et al. Ann Surg. 2019.

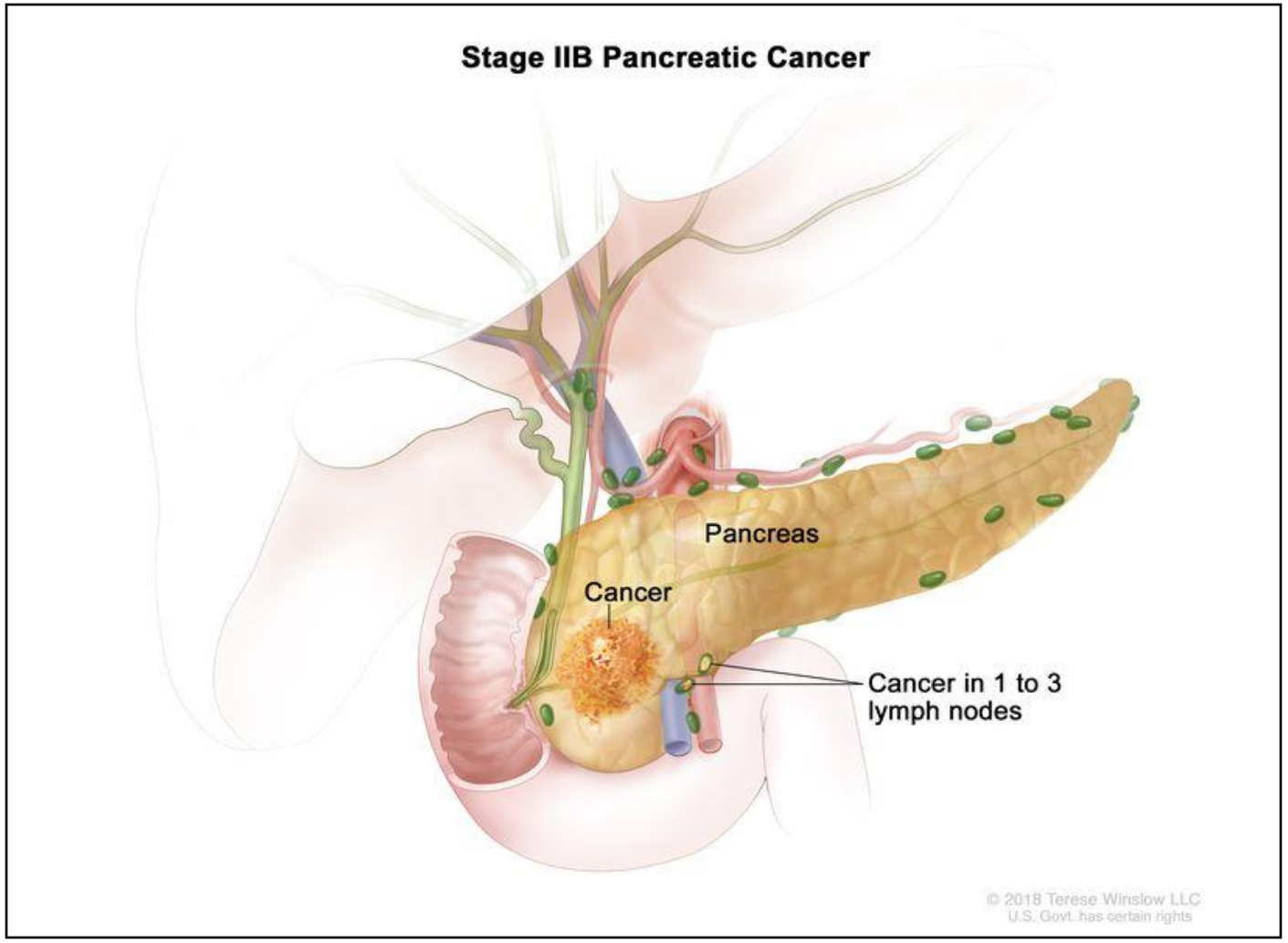
## Columbia University Cohort




Jamison and Manji, Unpublished

# Anatomy and Staging




**Unresectable**

Distant metastases

Arterial encasement (celiac trunk, superior mesenteric artery, or hepatic artery)

Arterial involvement (celiac trunk, superior mesenteric artery, or hepatic artery)

Venous encasement (portal or superior mesenteric vein)

Venous involvement (portal or superior mesenteric vein)

Attached to other organs

No arterial or venous involvement

**Resectable**

Locally Advanced

Borderline Resectable

Ryan DP et al., NEJM 2014;371:1039-1049
https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq#section/_139

Manji GA and Vollmer CM. ASCO Education. 2019.

# Definition of Resectable PDAC

National Comprehensive Cancer Network®

## NCCN Guidelines Version 2.2025
## Pancreatic Adenocarcinoma

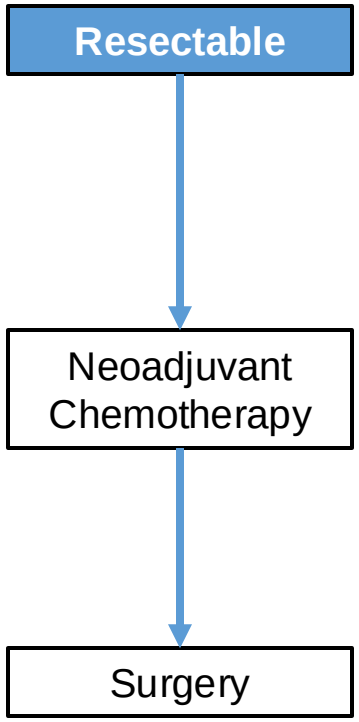
NCCN Guidelines Index
Table of Contents
Discussion

### CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

• Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

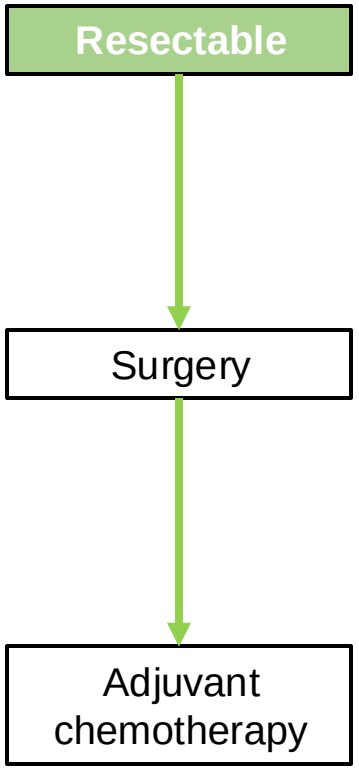
| Resectability Status | Arterial | Venous |
|---|---|---|
| Resectable | • No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). | • No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity. |
| Borderline Resectable[b] | Pancreatic head/uncinate process:<br>• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.<br>• Solid tumor contact with the SMA of ≤180°.<br>• Solid tumor contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning.<br>Pancreatic body/tail:<br>• Solid tumor contact with the CA of ≤180°. | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.<br>• Solid tumor contact with the inferior vena cava (IVC). |
| Locally Advanced[b,c,d] | Head/uncinate process:<br>• Solid tumor contact >180° with the SMA or CA.<br>Pancreatic body/tail:<br>• Solid tumor contact of >180° with the SMA or CA.<br>• Solid tumor contact with the CA and aortic involvement. | • Not currently amenable to resection and primary reconstruction due to complete occlusion of SMV/PV |

# Resectable PDAC – Neoadjuvant or Adjuvant Therapy



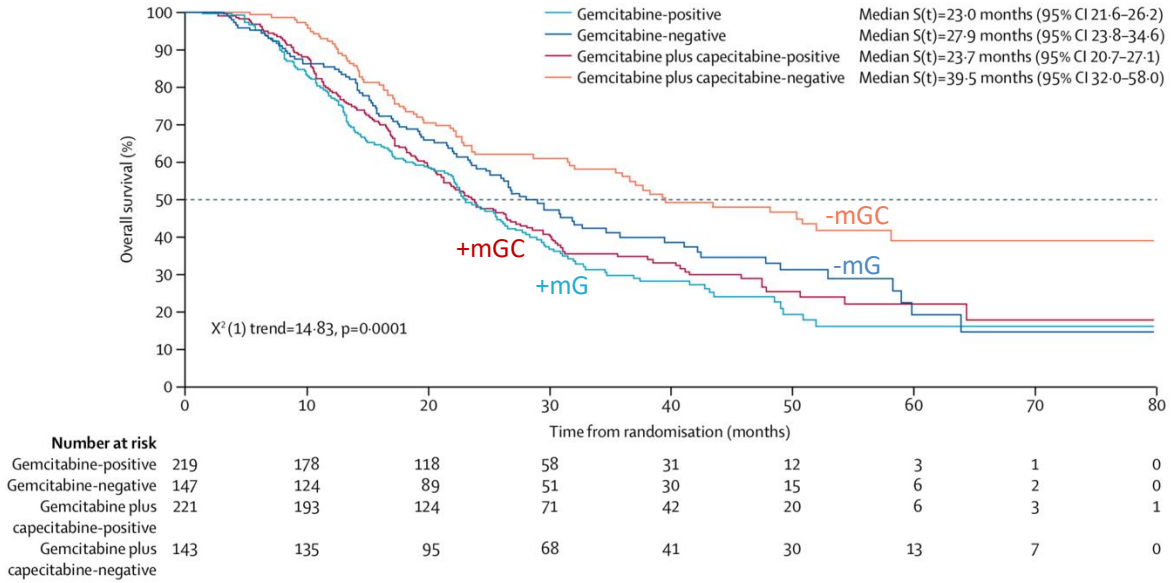

- To downstage tumor
- Decrease surgical complexity
- Treat micro-metastatic
- Chemotherapy tolerability

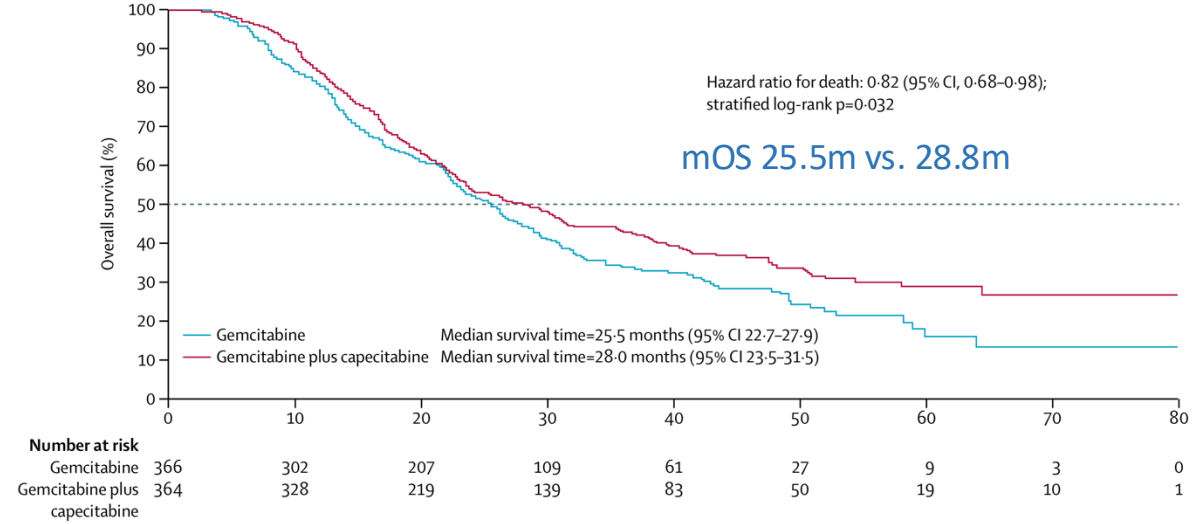
- Chemotherapy response?
  - Predictive markers
  - Disease progression
  - Window of opportunity
- Patient preference



# Role of Adjuvant Gemcitabine and Capecitabine

- ESPAC-4. Randomized phase 3 (N = 730)
- Resected pancreatic ductal adenocarcinoma
- Gemcitabine and Capecitabine or Gemcitabine for 24 weeks
- Primary Endpoint – Overall Survival

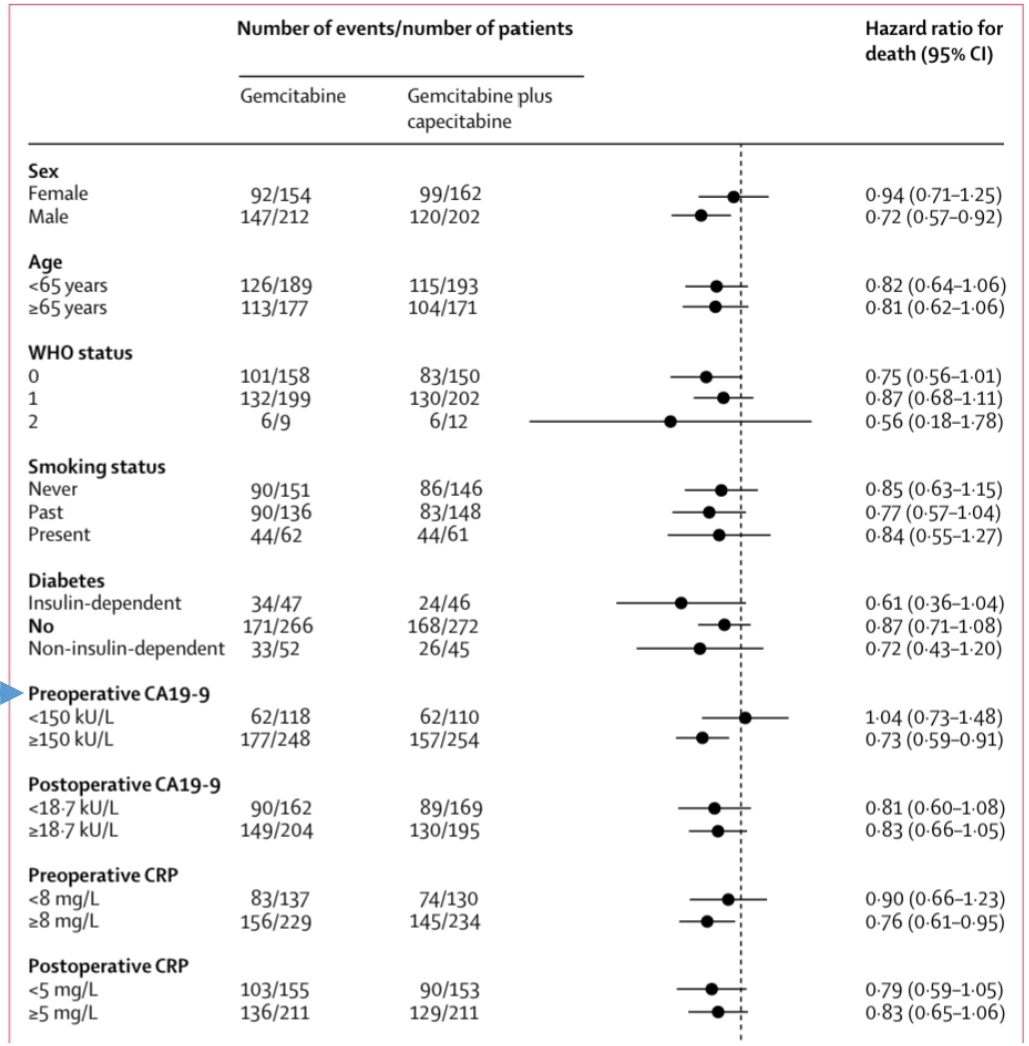




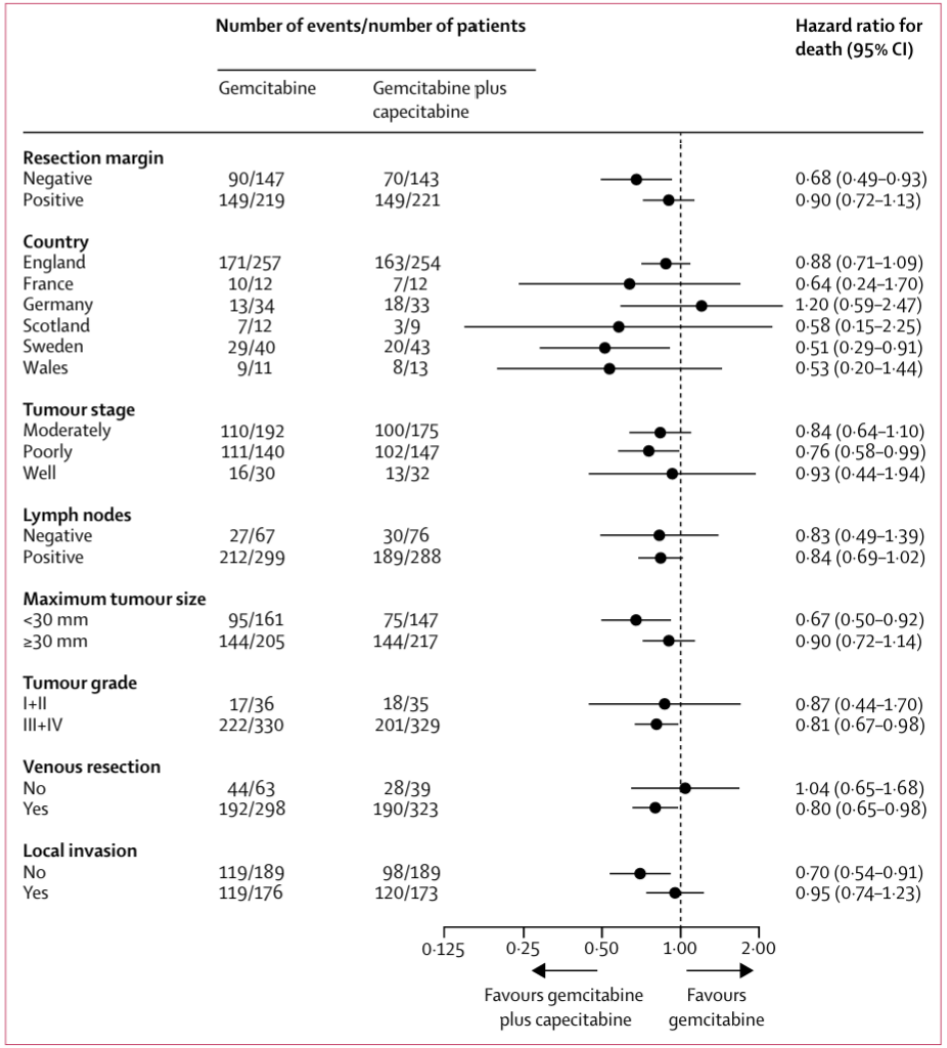

Neoptolemos JP, et al. Lancet. 2017;389:1011-24

# Role of Adjuvant Gemcitabine and Capecitabine



| | Number of events/number of patients | | Hazard ratio for death (95% CI) |
|---|---|---|---|
| | Gemcitabine | Gemcitabine plus capecitabine | |
| **Sex** | | | |
| Female | 92/154 | 99/162 | 0·94 (0·71–1·25) |
| Male | 147/212 | 120/202 | 0·72 (0·57–0·92) |
| **Age** | | | |
| <65 years | 126/189 | 115/193 | 0·82 (0·64–1·06) |
| ≥65 years | 113/177 | 104/171 | 0·81 (0·62–1·06) |
| **WHO status** | | | |
| 0 | 101/158 | 83/150 | 0·75 (0·56–1·01) |
| 1 | 132/199 | 130/202 | 0·87 (0·68–1·11) |
| 2 | 6/9 | 6/12 | 0·56 (0·18–1·78) |
| **Smoking status** | | | |
| Never | 90/151 | 86/146 | 0·85 (0·63–1·15) |
| Past | 90/136 | 83/148 | 0·77 (0·57–1·04) |
| Present | 44/62 | 44/61 | 0·84 (0·55–1·27) |
| **Diabetes** | | | |
| Insulin-dependent | 34/47 | 24/46 | 0·61 (0·36–1·04) |
| **No** | 171/266 | 168/272 | 0·87 (0·71–1·08) |
| Non-insulin-dependent | 33/52 | 26/45 | 0·72 (0·43–1·20) |
| **Preoperative CA19-9** | | | |
| <150 kU/L | 62/118 | 62/110 | 1·04 (0·73–1·48) |
| ≥150 kU/L | 177/248 | 157/254 | 0·73 (0·59–0·91) |
| **Postoperative CA19-9** | | | |
| <18·7 kU/L | 90/162 | 89/169 | 0·81 (0·60–1·08) |
| ≥18·7 kU/L | 149/204 | 130/195 | 0·83 (0·66–1·05) |
| **Preoperative CRP** | | | |
| <8 mg/L | 83/137 | 74/130 | 0·90 (0·66–1·23) |
| ≥8 mg/L | 156/229 | 145/234 | 0·76 (0·61–0·95) |
| **Postoperative CRP** | | | |
| <5 mg/L | 103/155 | 90/153 | 0·79 (0·59–1·05) |
| ≥5 mg/L | 136/211 | 129/211 | 0·83 (0·65–1·06) |

** Table modified.



| | Number of events/number of patients | | Hazard ratio for death (95% CI) |
|---|---|---|---|
| | Gemcitabine | Gemcitabine plus capecitabine | |
| **Resection margin** | | | |
| Negative | 90/147 | 70/143 | 0·68 (0·49–0·93) |
| Positive | 149/219 | 149/221 | 0·90 (0·72–1·13) |
| **Country** | | | |
| England | 171/257 | 163/254 | 0·88 (0·71–1·09) |
| France | 10/12 | 7/12 | 0·64 (0·24–1·70) |
| Germany | 13/34 | 18/33 | 1·20 (0·59–2·47) |
| Scotland | 7/12 | 3/9 | 0·58 (0·15–2·25) |
| Sweden | 29/40 | 20/43 | 0·51 (0·29–0·91) |
| Wales | 9/11 | 8/13 | 0·53 (0·20–1·44) |
| **Tumour stage** | | | |
| Moderately | 110/192 | 100/175 | 0·84 (0·64–1·10) |
| Poorly | 111/140 | 102/147 | 0·76 (0·58–0·99) |
| Well | 16/30 | 13/32 | 0·93 (0·44–1·94) |
| **Lymph nodes** | | | |
| Negative | 27/67 | 30/76 | 0·83 (0·49–1·39) |
| Positive | 212/299 | 189/288 | 0·84 (0·69–1·02) |
| **Maximum tumour size** | | | |
| <30 mm | 95/161 | 75/147 | 0·67 (0·50–0·92) |
| ≥30 mm | 144/205 | 144/217 | 0·90 (0·72–1·14) |
| **Tumour grade** | | | |
| I+II | 17/36 | 18/35 | 0·87 (0·44–1·70) |
| III+IV | 222/330 | 201/329 | 0·81 (0·67–0·98) |
| **Venous resection** | | | |
| No | 44/63 | 28/39 | 1·04 (0·65–1·68) |
| Yes | 192/298 | 190/323 | 0·80 (0·65–0·98) |
| **Local invasion** | | | |
| No | 119/189 | 98/189 | 0·70 (0·54–0·91) |
| Yes | 119/176 | 120/173 | 0·95 (0·74–1·23) |



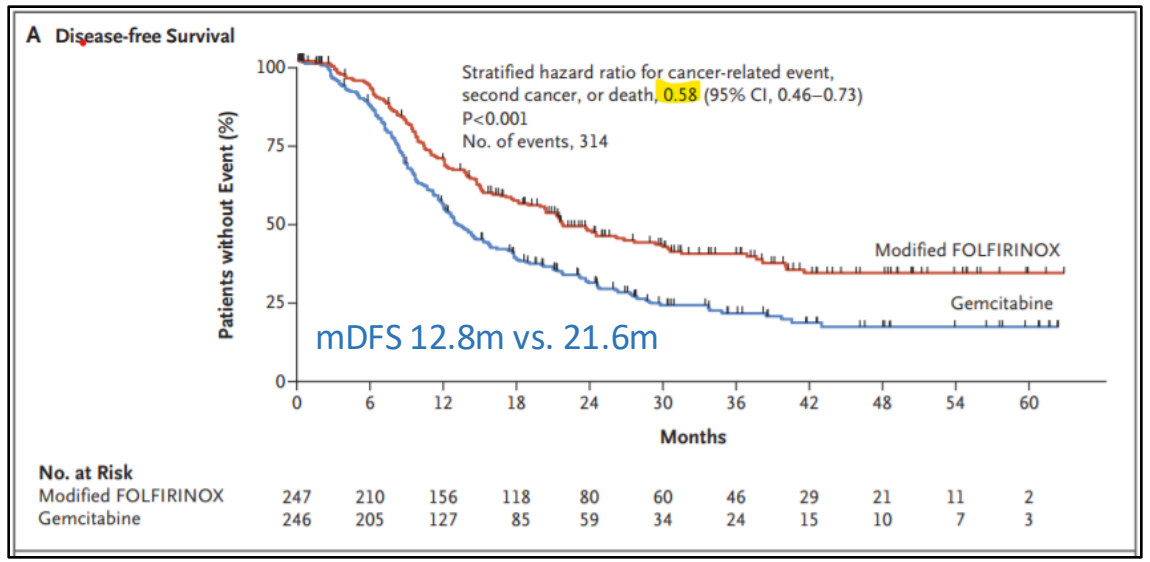
*Figure 3*: **Forest plot of the treatment effect on overall survival in prespecified subgroups**

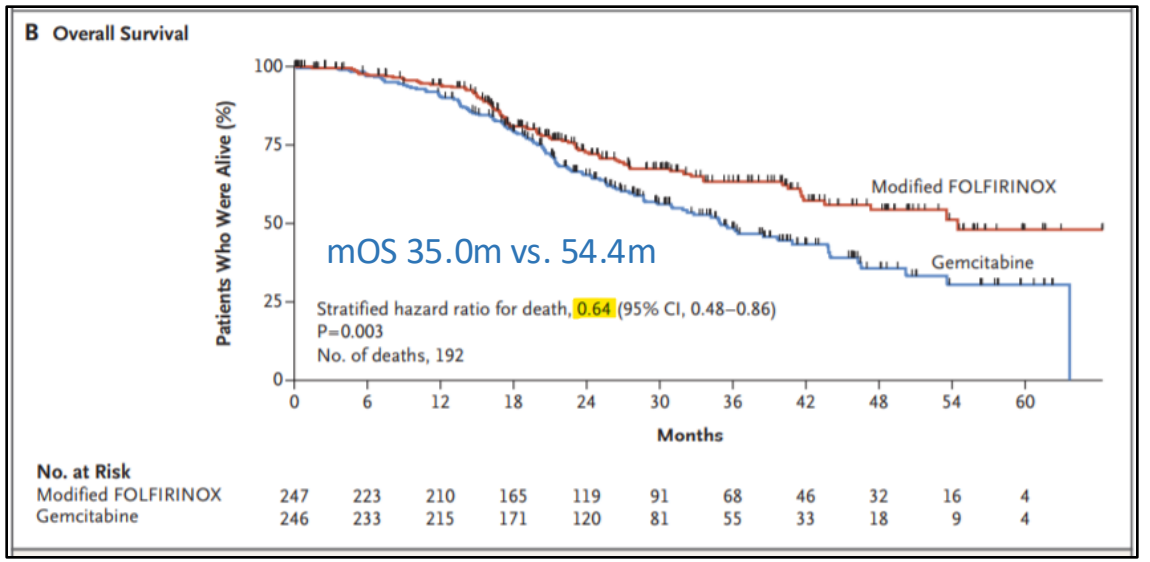


Neoptolemos JP, et al. Lancet. 2017;389:1011-24

# Role of Adjuvant modified FOLFIRINOX

- PRODIGE 24 – ACCORD. Randomized phase 3 (N = 493)
- Resected pancreatic ductal adenocarcinoma
- mFOLFIRINOX or Gemcitabine for 24 weeks
- Primary Endpoint – Disease-free Survival

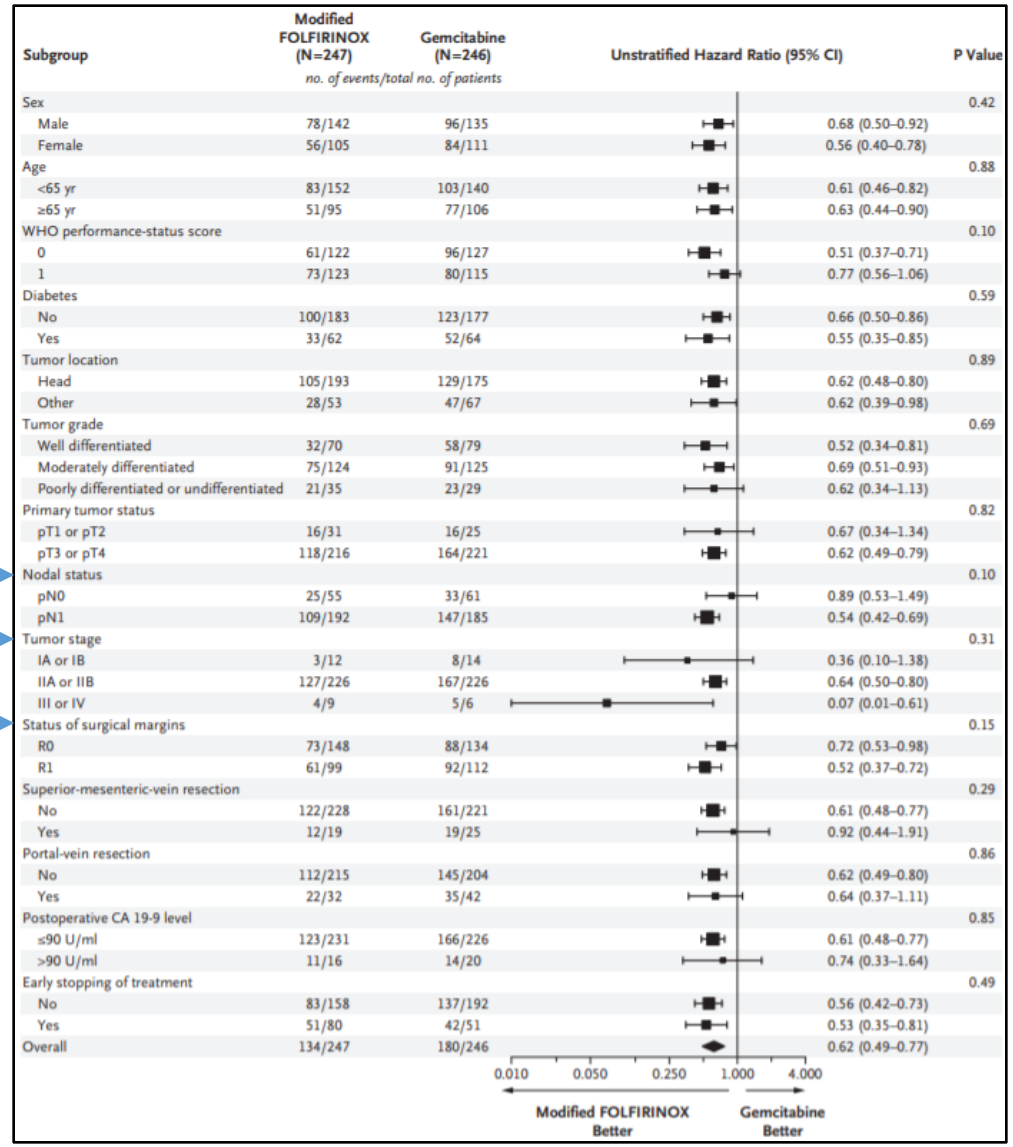





Conroy T, et al. N Engl J Med 2018;379:2395-406

# Role of Adjuvant modified FOLFIRINOX



| Subgroup | Modified FOLFIRINOX (N=247) | Gemcitabine (N=246) | Unstratified Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. of patients* | | | |
| Sex | | | | 0.42 |
| Male | 78/142 | 96/135 | 0.68 (0.50–0.92) | |
| Female | 56/105 | 84/111 | 0.56 (0.40–0.78) | |
| Age | | | | 0.88 |
| <65 yr | 83/152 | 103/140 | 0.61 (0.46–0.82) | |
| ≥65 yr | 51/95 | 77/106 | 0.63 (0.44–0.90) | |
| WHO performance-status score | | | | 0.10 |
| 0 | 61/122 | 96/127 | 0.51 (0.37–0.71) | |
| 1 | 73/123 | 80/115 | 0.77 (0.56–1.06) | |
| Diabetes | | | | 0.59 |
| No | 100/183 | 123/177 | 0.66 (0.50–0.86) | |
| Yes | 33/62 | 52/64 | 0.55 (0.35–0.85) | |
| Tumor location | | | | 0.89 |
| Head | 105/193 | 129/175 | 0.62 (0.48–0.80) | |
| Other | 28/53 | 47/67 | 0.62 (0.39–0.98) | |
| Tumor grade | | | | 0.69 |
| Well differentiated | 32/70 | 58/79 | 0.52 (0.34–0.81) | |
| Moderately differentiated | 75/124 | 91/125 | 0.69 (0.51–0.93) | |
| Poorly differentiated or undifferentiated | 21/35 | 23/29 | 0.62 (0.34–1.13) | |
| Primary tumor status | | | | 0.82 |
| pT1 or pT2 | 16/31 | 16/25 | 0.67 (0.34–1.34) | |
| pT3 or pT4 | 118/216 | 164/221 | 0.62 (0.49–0.79) | |
| Nodal status | | | | 0.10 |
| pN0 | 25/55 | 33/61 | 0.89 (0.53–1.49) | |
| pN1 | 109/192 | 147/185 | 0.54 (0.42–0.69) | |
| Tumor stage | | | | 0.31 |
| IA or IB | 3/12 | 8/14 | 0.36 (0.10–1.38) | |
| IIA or IIB | 127/226 | 167/226 | 0.64 (0.50–0.80) | |
| III or IV | 4/9 | 5/6 | 0.07 (0.01–0.61) | |
| Status of surgical margins | | | | 0.15 |
| R0 | 73/148 | 88/134 | 0.72 (0.53–0.98) | |
| R1 | 61/99 | 92/112 | 0.52 (0.37–0.72) | |
| Superior-mesenteric-vein resection | | | | 0.29 |
| No | 122/228 | 161/221 | 0.61 (0.48–0.77) | |
| Yes | 12/19 | 19/25 | 0.92 (0.44–1.91) | |
| Portal-vein resection | | | | 0.86 |
| No | 112/215 | 145/204 | 0.62 (0.49–0.80) | |
| Yes | 22/32 | 35/42 | 0.64 (0.37–1.11) | |
| Postoperative CA 19-9 level | | | | 0.85 |
| ≤90 U/ml | 123/231 | 166/226 | 0.61 (0.48–0.77) | |
| >90 U/ml | 11/16 | 14/20 | 0.74 (0.33–1.64) | |
| Early stopping of treatment | | | | 0.49 |
| No | 83/158 | 137/192 | 0.56 (0.42–0.73) | |
| Yes | 51/80 | 42/51 | 0.53 (0.35–0.81) | |
| Overall | 134/247 | 180/246 | 0.62 (0.49–0.77) | |





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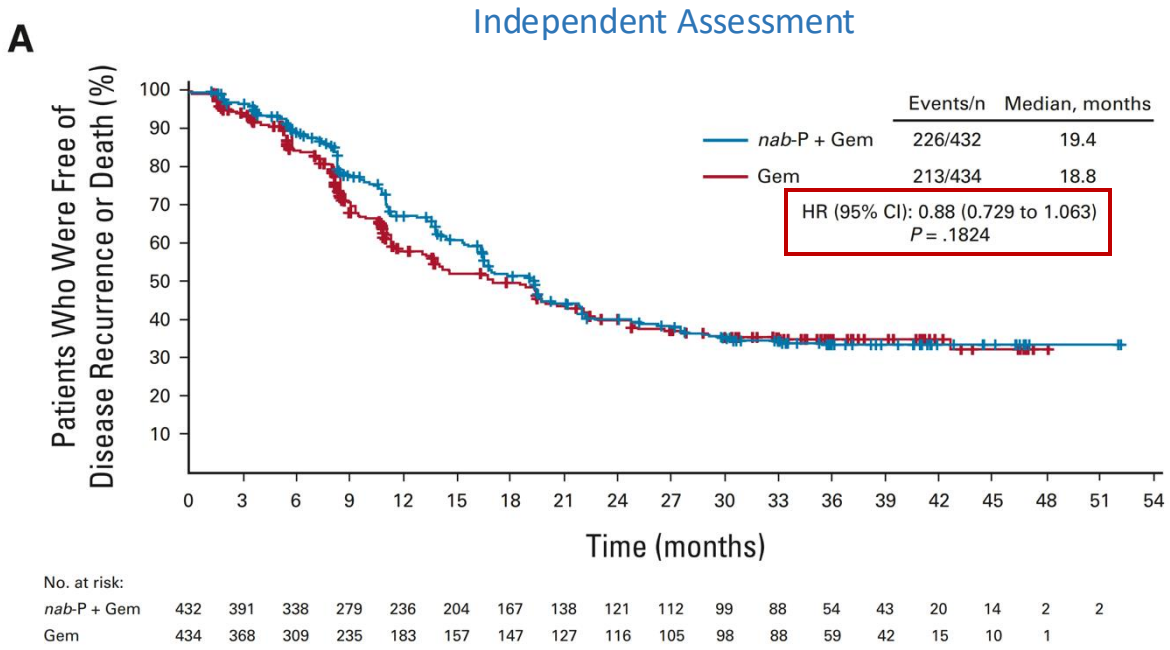
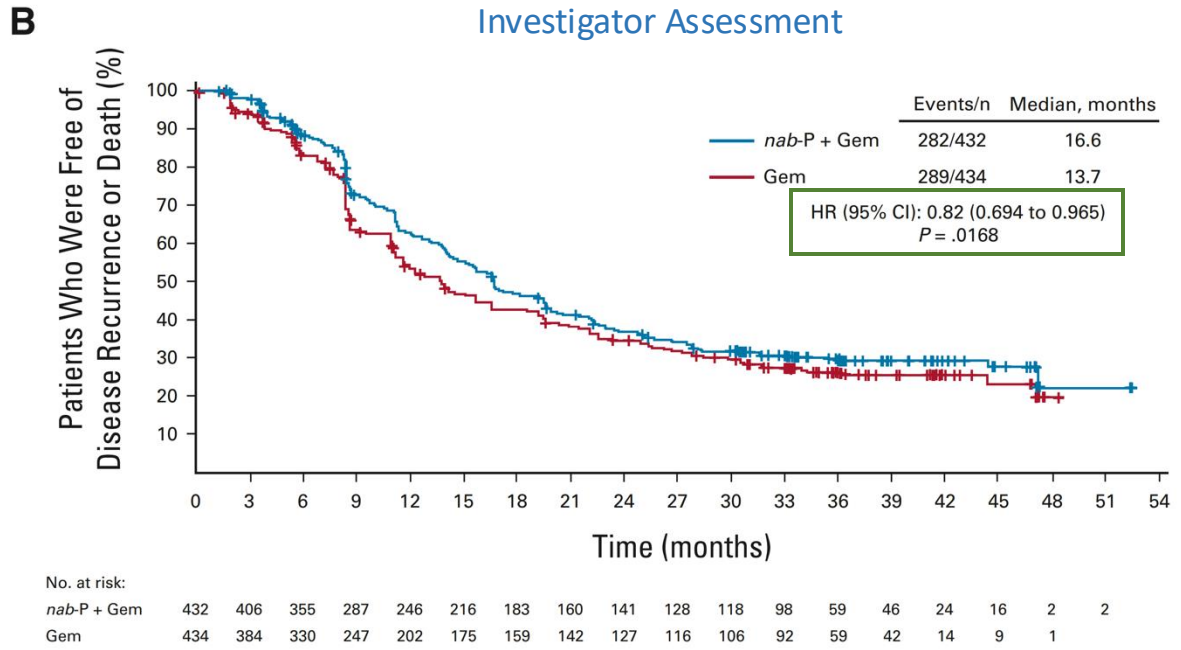
# Role of Adjuvant Gemcitabine and *nab*-Paclitaxel

- APACT. Randomized phase 3 (N = 866)
- Resected pancreatic ductal adenocarcinoma
- Gemcitabine and nab-Paclitaxel or Gemcitabine for 24 weeks
- Primary Endpoint – Independently assessed disease-free survival



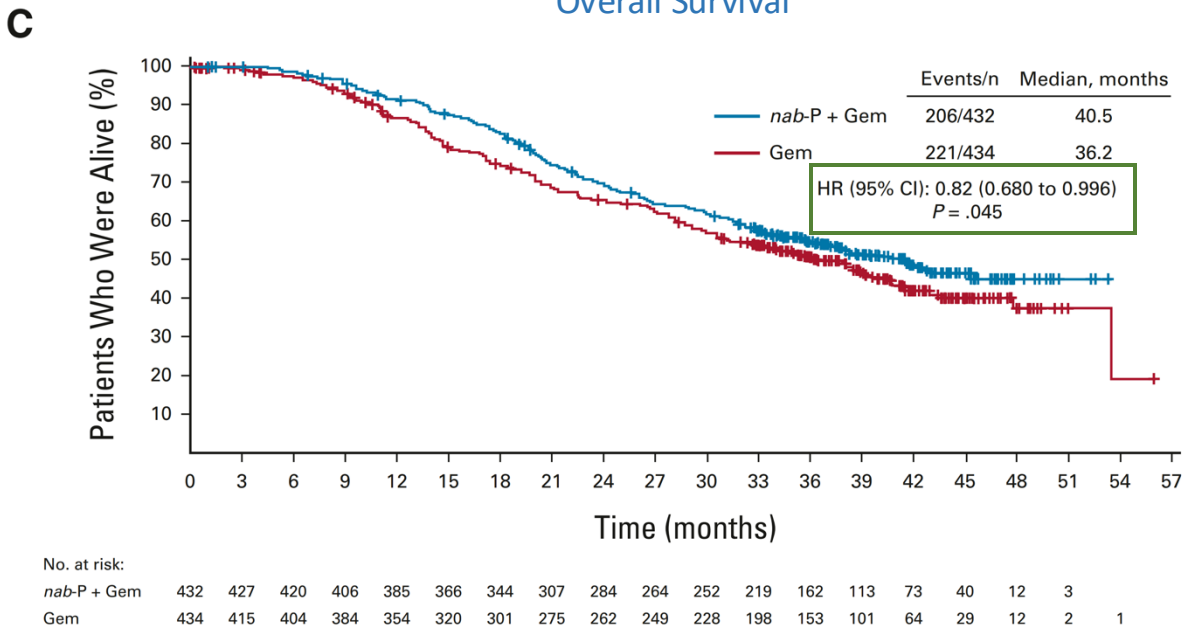






Tempero MA, et al. JCO 2018;379:2395-406

# Role of Adjuvant Gemcitabine and nab-Paclitaxel

## Overall Survival




## Investigator Assessment

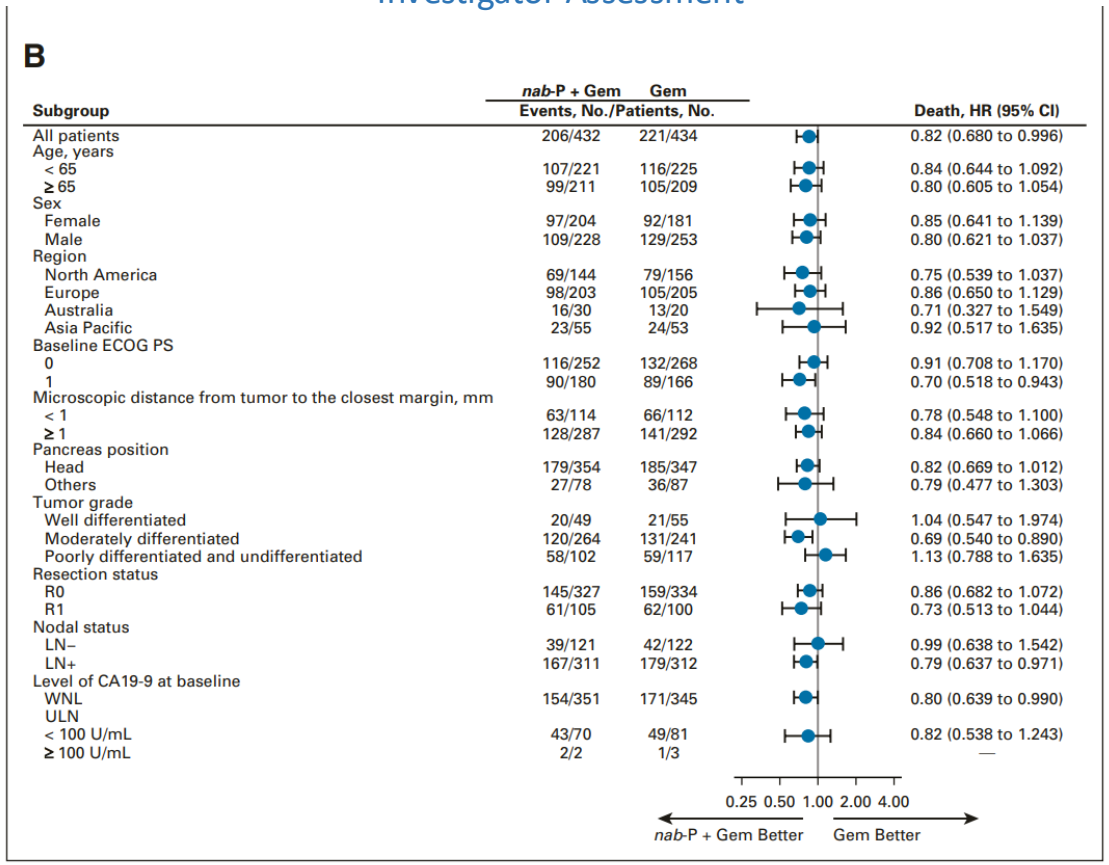



**FIG 3.** Forest plot subgroup analysis of DFS and OS. At the primary data cutoff (December 31, 2018), prespecified (A) blinded, independent, centrally reviewed DFS and (B) OS. CA19-9, carbohydrate antigen 19-9; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status, Gem, gemcitabine; HR, hazard ratio; LN, lymph node; *nab*-P, *nab*-paclitaxel; OS, overall survival; ULN, upper limit of normal; WNL, within normal limits.



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# Role of Adjuvant Chemotherapy

**TABLE 1.** Efficacy of Adjuvant Therapies in Pancreas Adenocarcinoma

| Trial | Experimental Therapy | Comparator | Primary End Point | Median Follow-Up, Months | DFS, Months | OS, Months | 5-Years Survival Rate, %; Exp *v* Comp |
|---|---|---|---|---|---|---|---|
| ESPAC-1[6] | 5-FU+ leucovorin | Observation | 2-year survival rate | 47 (32-62) | 15.3 (10.5-19.2) *v* 9.4 (8.4-15.2) | 20.1 (16.5-22.7) *v* 15.5 (13.0-17.7) | 21 *v* 8[a] |
| CONKO-001[7] | Gemcitabine | Observation | DFS | 136 (104- 144) | 13.4 (11.6-15.3) *v* 6.7 (6.0-7.5) | 22.8 (18.5-27.2) *v* 20.2 (17.7-22.8) | 20.7 (14.7-26.6) *v* 10.4 (5.9-15.0) |
| JASPAC-01[8] | S-1 | Gemcitabine | OS | 79.3 (72.0-89.0) *v*. 82.3 (71.8-88.5) | 22.9 (17.4-30.6) *v* 11.3 (9.7-13.6)[b] | 46.5 (37.8-63.7) *v* 25.5 (22.5-29.6) | 44.1 (36.9-51.1) *v* 24.4 (18.6-30.8)[a] |
| ESPAC-4[9] | Gemcitabine and capecitabine | Gemcitabine | OS | 43.2 (39.7-45.5) | 13.9 (12.1-16.6) *v* 13.1 (11.6-15.3) | 28.0 (23.5-31.5) *v* 25.5 (22.7-27.9) | 28.8 (10.2-23.7) *v* 16.3 (10.2-23.7)[a] |
| PRODIGE24/CCTG[10] | mFOLFIRINOX | Gemcitabine | DFS | 69.7 (59.4-84.1) | 21.4 (9.9-70.0) *v* 12.8 (7.9-29.8) | 53.5 (22.4-NE) *v* 35.5 (20.3-80.8) | 43.2 (36.5-49.7) *v* 31.4 (25.5-37.5) |
| APACT[1] | Gemcitabine and nab-paclitaxel | Gemcitabine | Independently assessed DFS[3] | 63.2 (60.1-68.7) | 19.4 (16.6-21.9) *v* 18.8 (13.8-20.3)[c] Investigator-assessed DFS (Secondary Endpoint) 16.6 (14.6-19.3) *v* 13.7 (11.2-16.0)[d] | 41.8 *v* 37.7 (HR, 0.80 (0.68-0.95; $P = .0091$) | 38 *v* 31[a] |

Abbreviations: 5-FU, fluorouracil; CCTG, Canadian Cancer Trials Group; Comp, comparator; DFS, disease-free survival; Exp, experimental; HR, hazard ratio; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; NE, nonestimable; OS, overall survival, PFS, progression free survival.

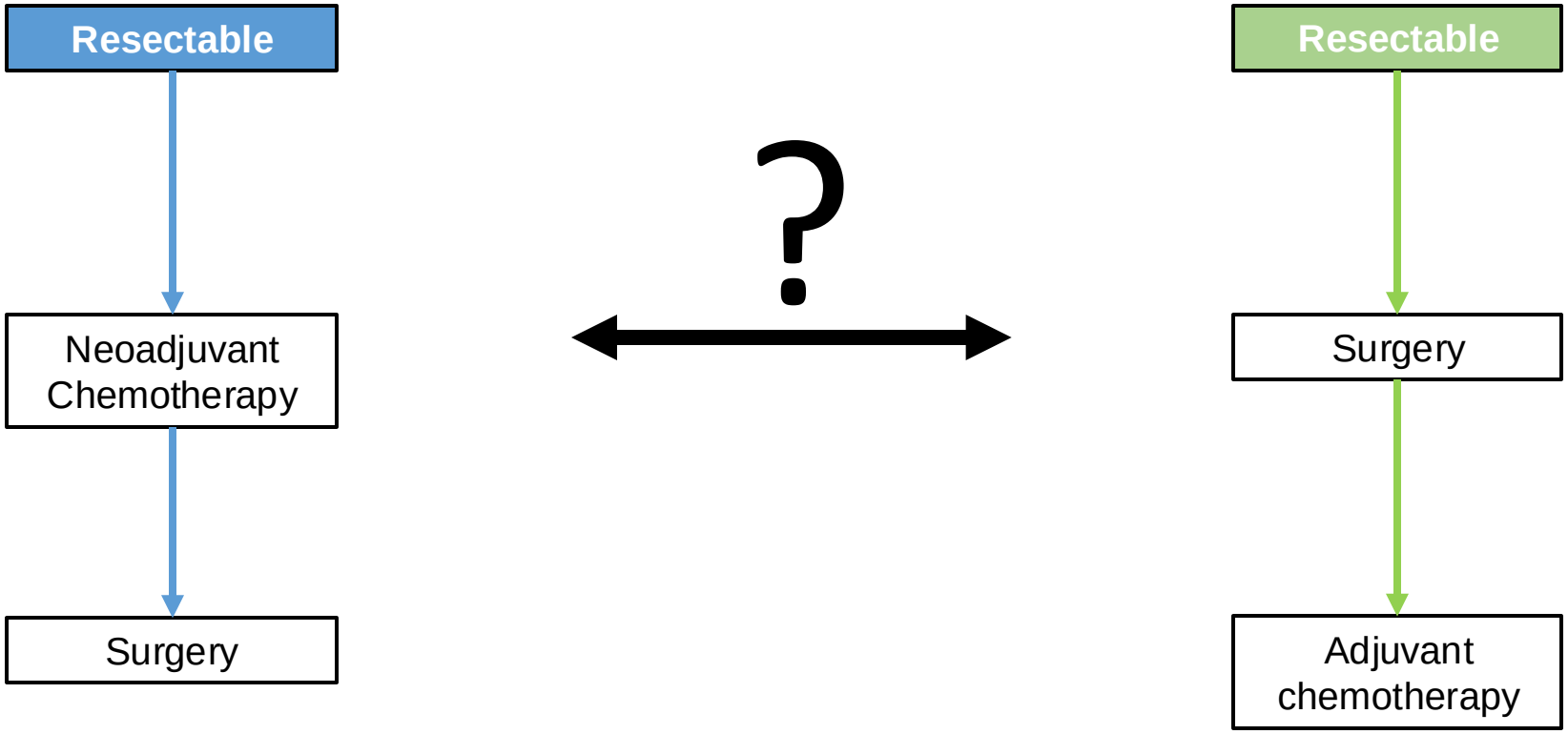
[a]5-year survival estimate.

[b]Relapse-free survival.

[c]Independently assessed DFS.

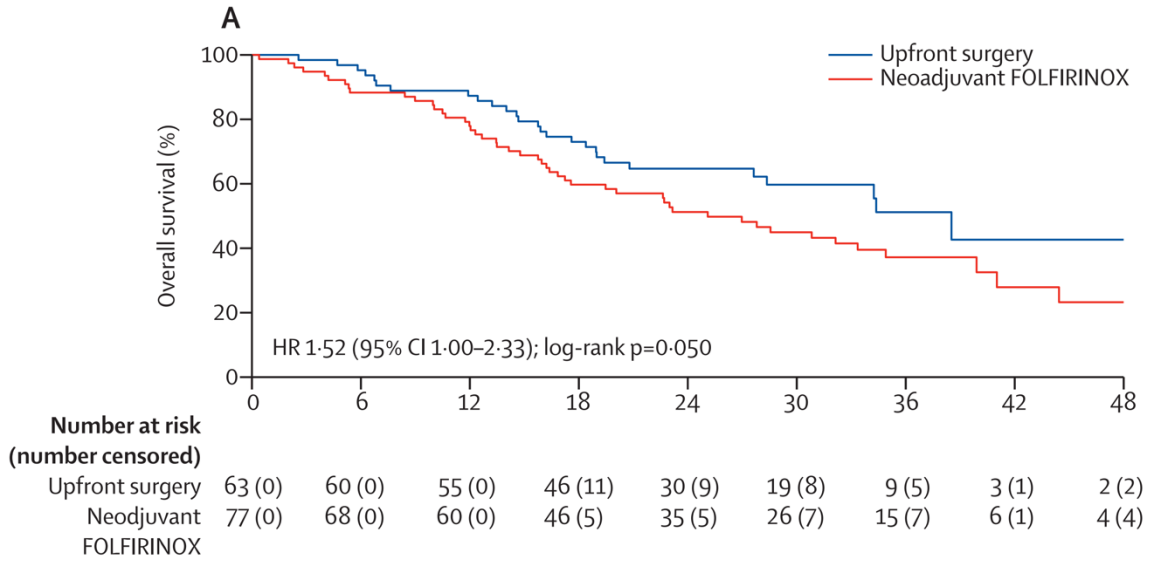
[d]Investigator-assessed DFS.

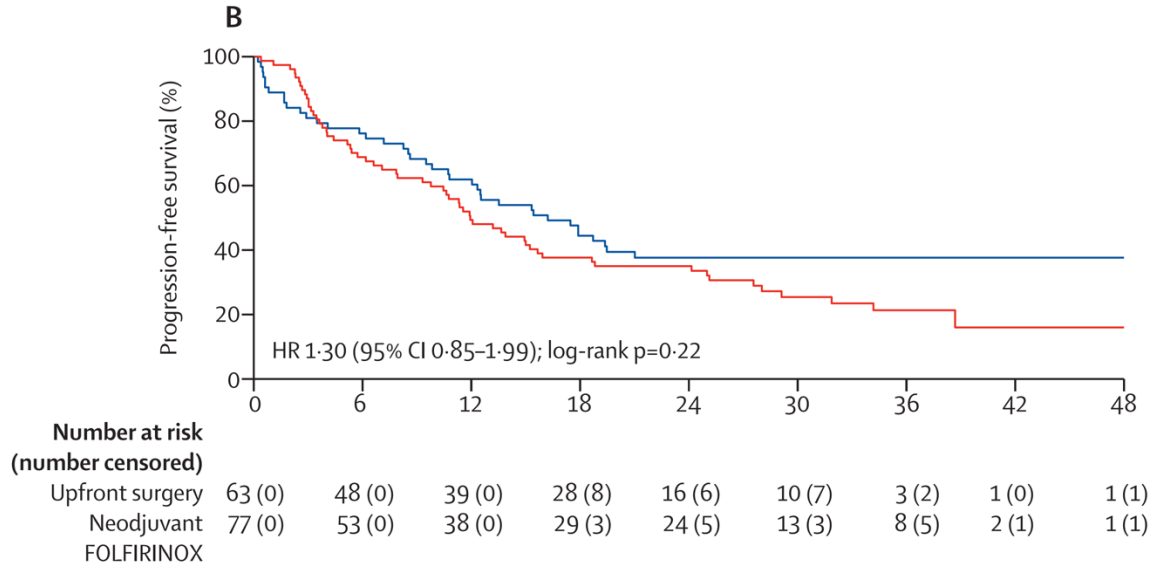
# Resectable PDAC – Neoadjuvant or Adjuvant Therapy



# FOLFIRINOX versus Upfront Surgery

- NORPACT-1. Randomized phase 2 (N = 866)
- Radiological evidence of pancreas head strongly suspected to PDAC
- FOLFIRINOX (4 cycles) followed by surgery and adjuvant chemotherapy **versus** upfront surgery followed by adjuvant chemotherapy
- Primary Endpoint – Overall survival at 18 months






Labori KJ, et al. Lancet Gastroenterol Hepatol. 2024; 9:205-17.

# FOLFIRINOX versus Upfront Surgery

| | Neoadjuvant FOLFIRINOX group (n=77) | Upfront surgery group (n=63) | HR or RR (95 % CI) | p value |
|---|---|---|---|---|
| **Primary endpoint (intention to treat)** | | | | |
| Proportion alive at 18 months (95% CI) | 60% (49–71) | 73% (62–84) | .. | 0·032 |
| **Secondary endpoints (intention to treat)** | | | | |
| Median (95% CI) overall survival, months | 25·1 (17·2–34·9) | 38·5 (27·6–NR) | HR 1·52 (1·00–2·33) | 0·050 |
| Median (95% CI) progression-free survival, months | 11·9 (9·3–15·7) | 16·2 (10·8–21·0) | HR 1·30 (0·85–1·99) | 0·22 |
| Proportion alive and disease free at 18 months (95% CI) | 38% (27–49) | 44% (32–57) | .. | 0·35 |
| Underwent resection | 63 (82%) | 56 (89%) | RR 0·92 (0·80–1·06) | 0·24 |
| Causes of not undergoing resection | | | | |
| Metastasis diagnosed preoperatively | 4 | 1 | .. | .. |
| Metastasis diagnosed intraoperatively | 8 | 6 | .. | .. |
| Toxicity during neoadjuvant chemotherapy | 2 | 0 | .. | .. |
| Adjuvant chemotherapy initiation | 51 (66%) | 47 (75%) | RR 0·89 (0·74–1·07) | 0·21 |
| Adjuvant chemotherapy completion | 41 (53%) | 31 (49%) | RR 1·12 (0·86–1·45) | 0·40 |
| Chemotherapy receipt (neoadjuvant, adjuvant, or both) | 73 (95%) | 47 (75%) | RR 1·27 (1·11–1·46) | 0·0006 |



Labori KJ, et al. Lancet Gastroenterol Hepatol. 2024; 9:205-17.

# ChemoRT versus Upfront Surgery

- PREOPANC. Randomized phase 3 (N = 246)
- Resectable and borderline resectable PDAC

  Chemo RT – Gem C1, Gem C2, Gem/RT C3 → Surgery → Gem C4 – C7

  Upfront Surgery – Surgery → Gem C4 – C7

- Primary Endpoint – Overall survival at18 months

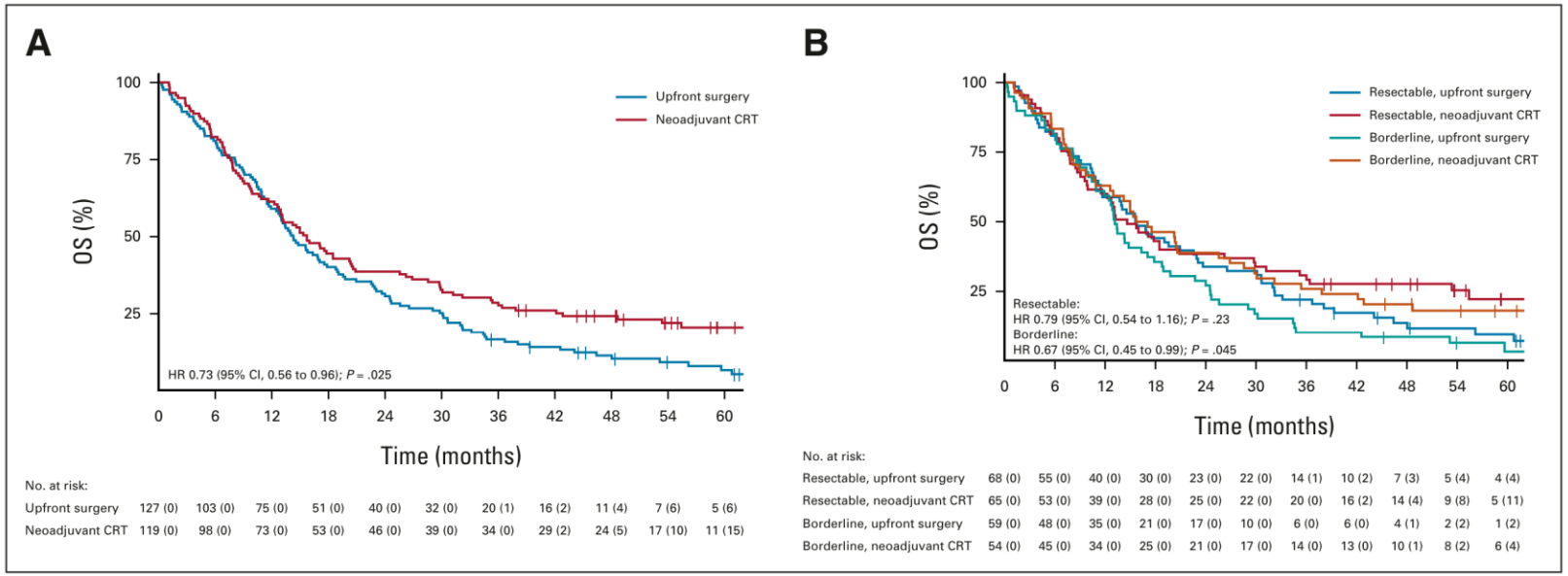



**FIG 2.** Kaplan-Meier estimates of OS by (A) treatment group and (B) by resectability and treatment group. CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival.



Versteijne E, et al. 2022; 40:1220-30

# ChemoRT versus Upfront Surgery

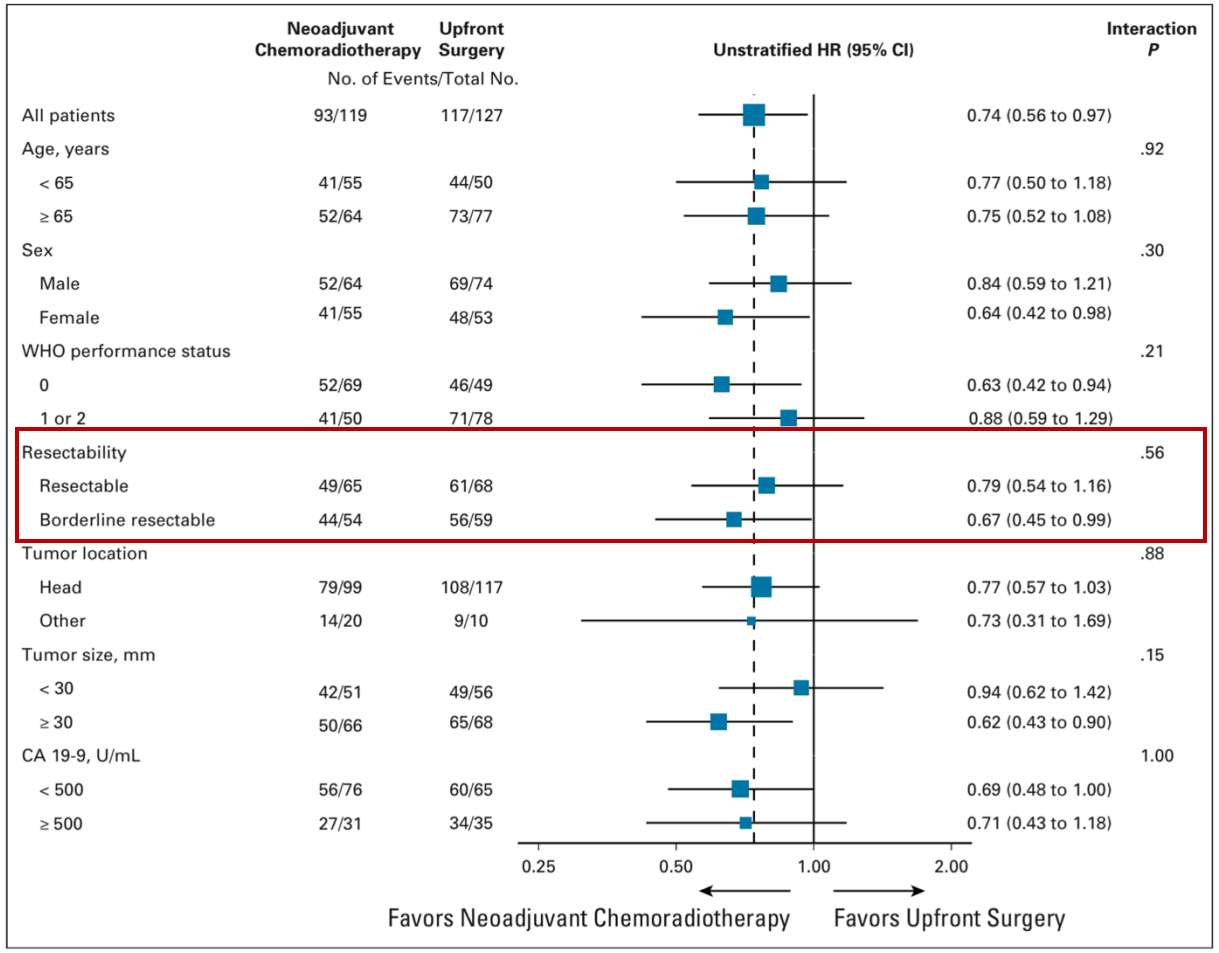



**FIG 3.** Forest plot of treatment effect on overall survival according to baseline characteristics of patients. The position of each square represents the point estimate of the treatment effect in the subgroup, and error bars represent 95% CIs. The sizes of the squares are proportional to the number of patients. The dashed line represents the unstratified HR for all patients. Tumor size was missing for five patients. CA 19-9 was missing for 39 patients. CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio.

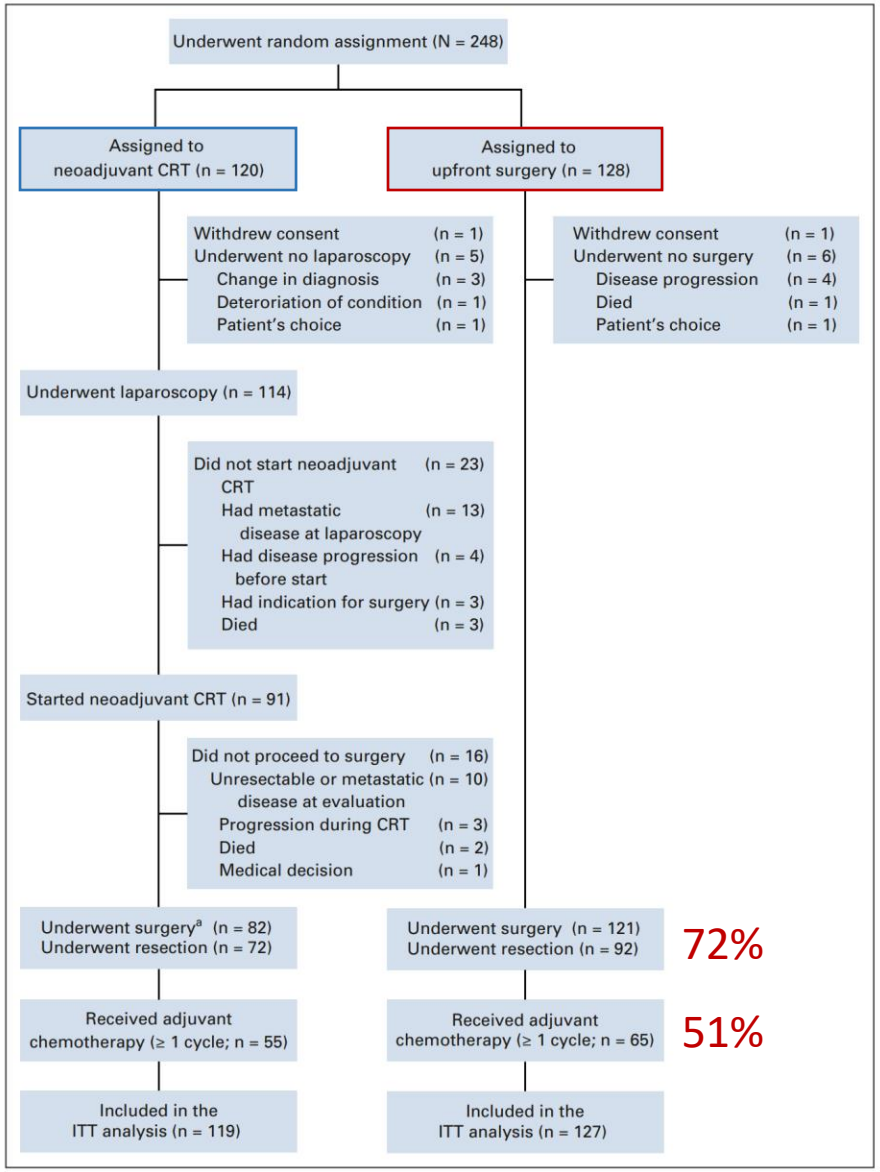



**FIG 1.** CONSORT diagram. [a]Seven patients proceeded to surgery without neoadjuvant chemoradiotherapy. CRT, chemoradiotherapy; ITT, intention-to-treat.



Versteijne E, et al. 2022; 40:1220-30

# Treatment Algorithm for Resectable PDAC

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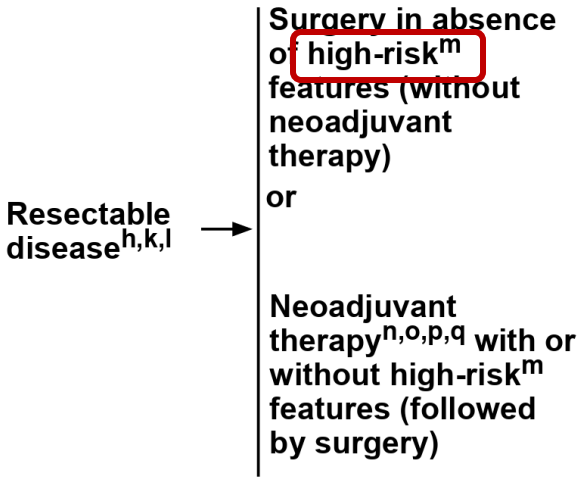


## High-risk Features

Equivocal or indeterminate imaging findings
Markedly elevated CA 19-9
Large primary tumors
Large regional lymph nodes
Excessive weight loss
Extreme pain

# Treatment Algorithm for Resectable PDAC

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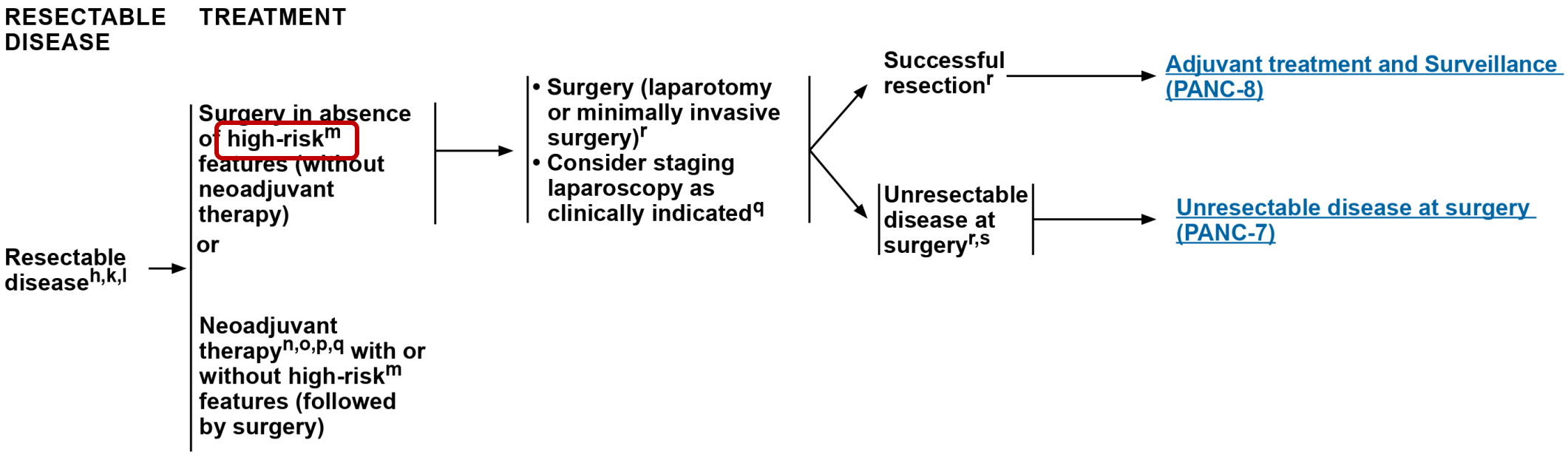


**High-risk features** – Equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain.

# Treatment Algorithm for Resectable PDAC

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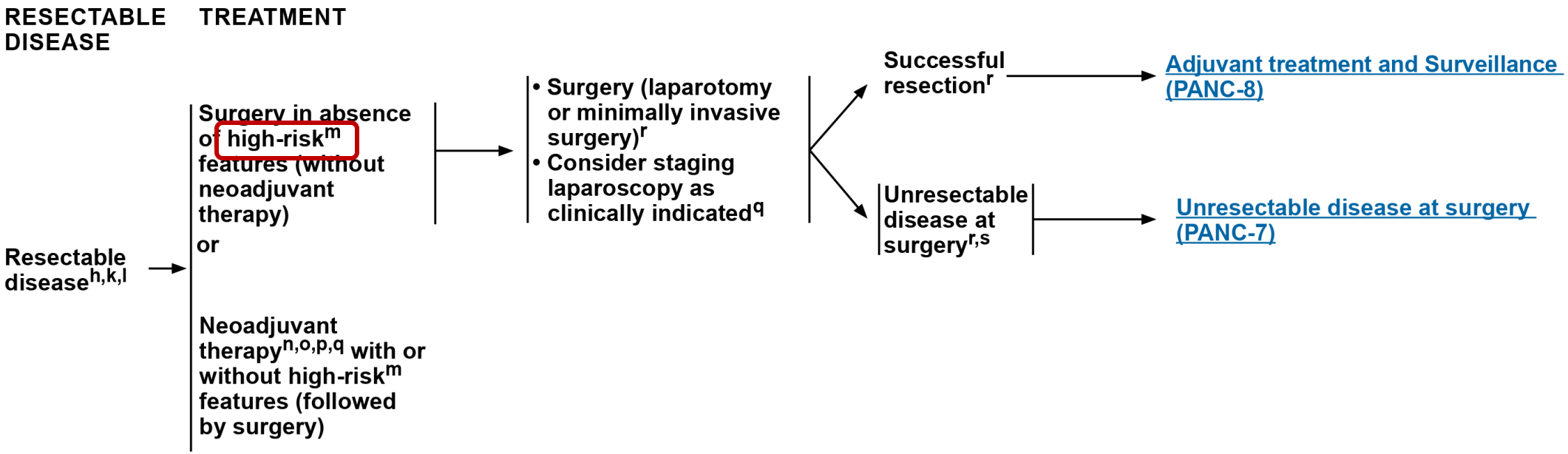


**High-risk features** – Equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain.

# Treatment Algorithm for Resectable PDAC

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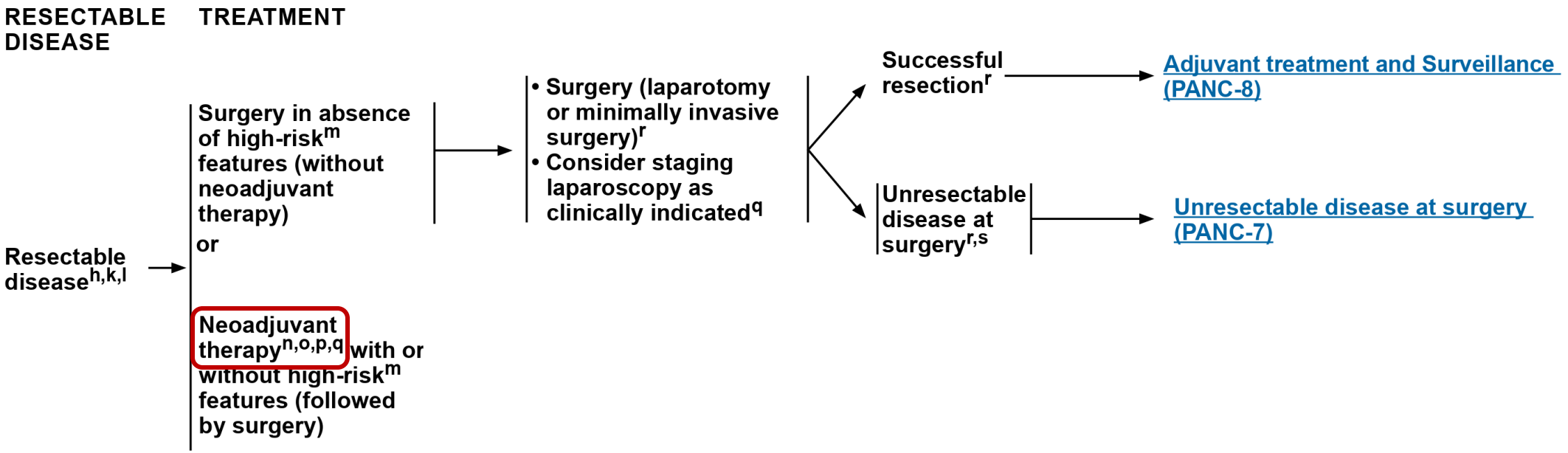


**For Neoadjuvant Therapy** – Consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging.

# Treatment Algorithm for Resectable PDAC

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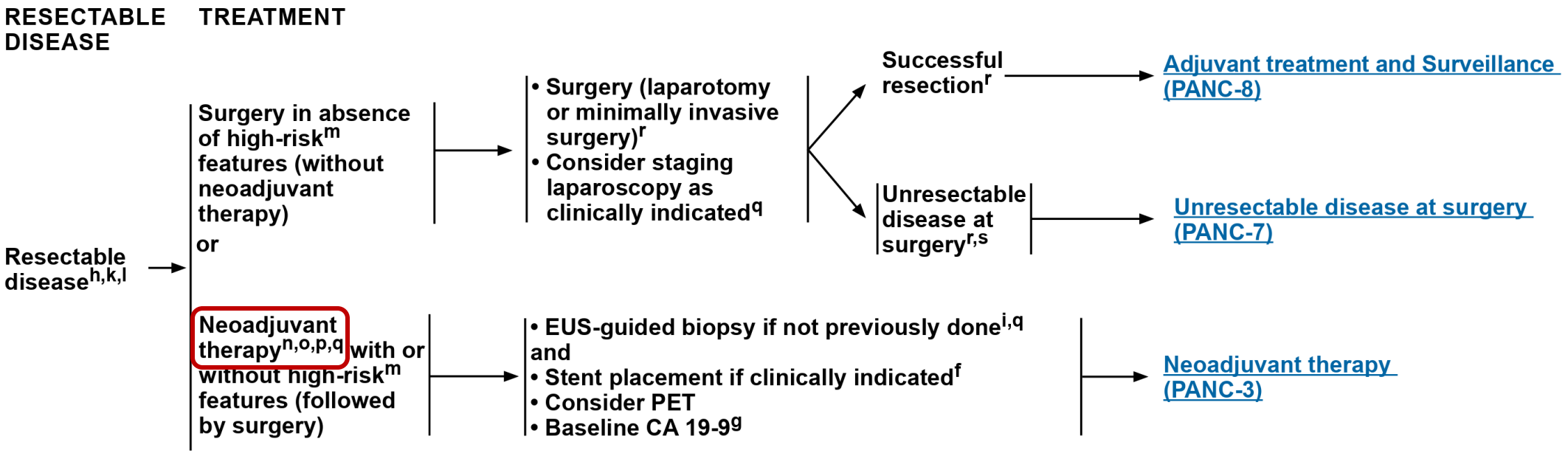


**For Neoadjuvant Therapy** – Consider PET/CT or PET/MRI scan before and after initiation to assess response to systemic therapy and for restaging..

# Treatment Algorithm for Resectable PDAC

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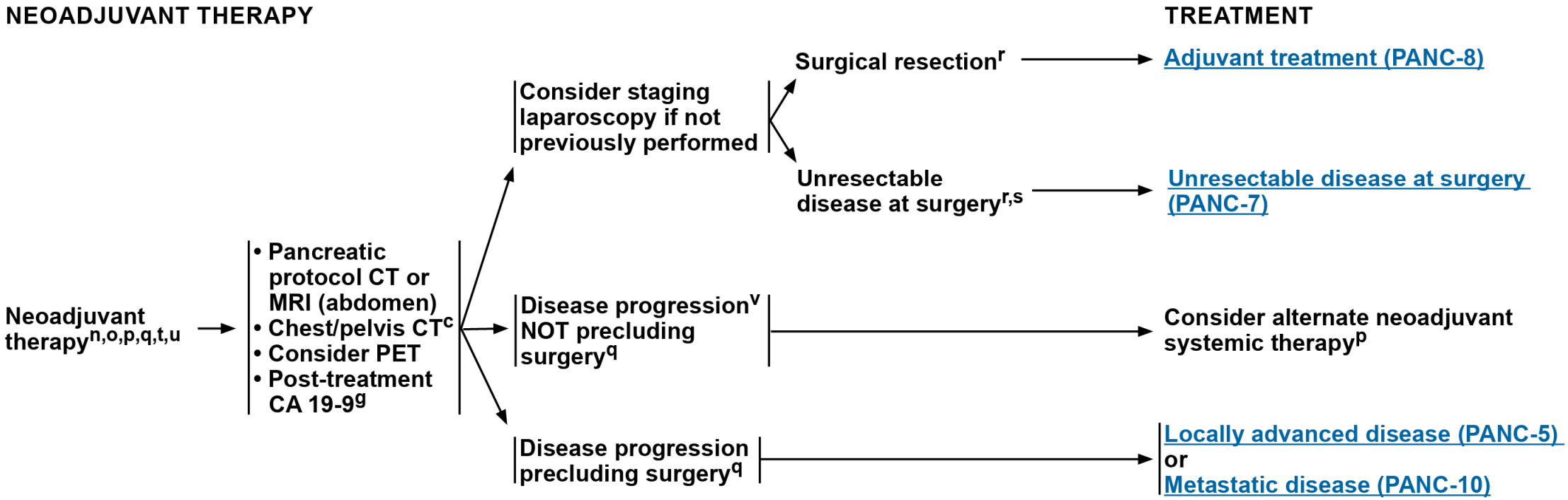

# Outcomes – Margin Status and Nodal Status

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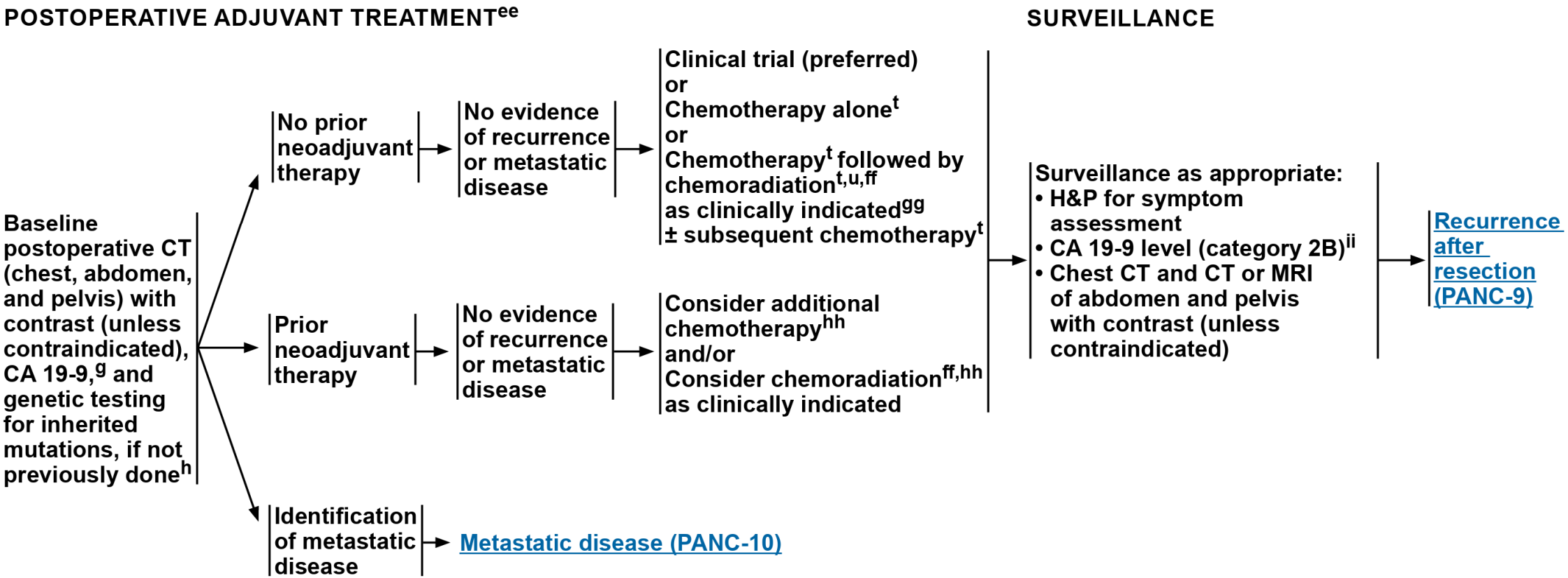

# Thank You